DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF NOVEL ORGANOSILICON AND ORGANOBORON COMPOUNDS

Dissertation submitted to
Visvesvaraya National Institute of Technology, Nagpur
in partial fulfillment of the requirements for the award of
the degree

Master of Science
in
Chemistry

by

Mohammed Nishad K (MS23CHM017)

Under the guidance of

Dr. Sandipan Halder

Department of Chemistry
Visvesvaraya National Institute of Technology
Nagpur 440 010 (India)

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Department of Chemistry

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Declaration

I, Mohammed Nishad K, hereby declare that this dissertation titled **"Design, synthesis, and biological evaluation of novel organosilicon and organoboron compounds"** was carried out by me in the Department of Chemistry of Visvesvaraya National Institute of Technology, Nagpur. The work is original and has not been submitted earlier, whole or in part, for the award of any degree/diploma at this or any other Institution / University.

Mohammed Nishad K
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Acknowledgements

I would like to express my heartfelt gratitude to my guide, **Dr. Sandipan Halder,** Assistant Professor, Department of Chemistry, Visvesvaraya National Institute of Technology, Nagpur, for giving me the opportunity and guidance to carry out my M.Sc. project under him and for his great leadership, constant encouragement, and wise mentoring during this study project. His knowledge and support have been crucial to both the success of my thesis and my academic development.

I would like to thank **Dr. Sujit K. Ghosh,** Head of the Department of Chemistry, VNIT, and **Dr. Premlal Patel**, Director of VNIT, for providing me with the necessary facilities for the completion of my project work.

I am very grateful to **Mr. Supratim Halder**, Research Scholar, Department of Chemistry, VNIT, for his support and for giving me new ideas throughout the duration, which were necessary for my project. His valuable advice and knowledge have helped me a lot throughout my project.

To all my PhD seniors and lab mates, **Mr. Sibasish Manna, Ms. Swati,** and **Ms. Kriti Jain,** thank you for your support, teamwork, and love for learning. Working with you has made my research journey special. I will always remember. I'm truly grateful to have shared this time with you.

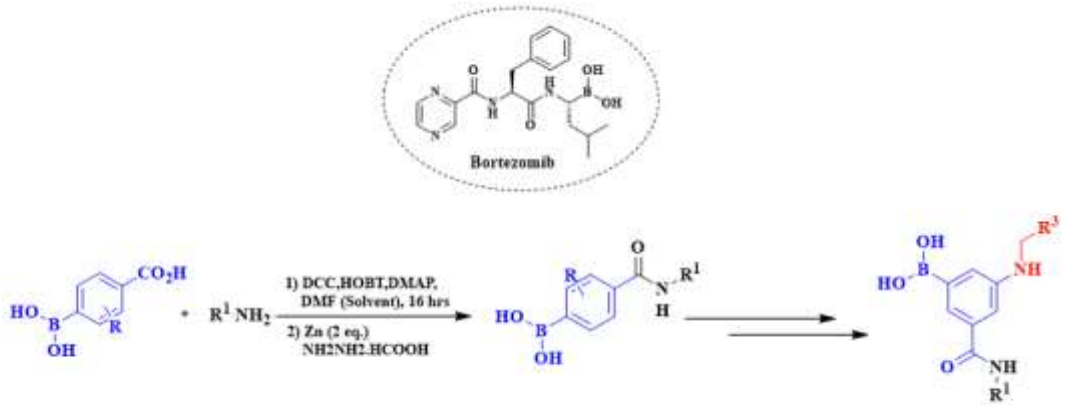
From the bottom of my heart, I am extremely heartful to my parents, **Mr. Mohammed Kutty K, Mrs. Ayishabeebi K** and family members, who supported me without their constant support, encouragement, and unconditional love, this journey would not have been possible.

Lastly, I extend my gratitude to all individuals who have contributed to this research endeavor, whether through participation, collaboration, or moral support. Your contributions have enriched the quality of this work and made this journey truly meaningful.

Mohammed Nishad K

Abstract

In the past, boron-containing organic compounds were viewed with caution in medicinal chemistry due to concerns about their potential toxicity. However, this perception has changed, especially after the approval of Bortezomib[1], anti-cancer drug used to treat multiple myeloma, which significantly boosted interest in these compounds, particularly the research on boronic acids as drugs for a variety of illnesses. Recent studies have highlighted boronic acids various biological applications, including potential anticancer, antibacterial, and antiviral properties[2]. Moreover, the commercial availability and uncomplicated synthetic methods make these compounds accessible for research and development.



This work focuses on the synthesis and study of various acyclic boronic acid containing drug candidates through the modification of functional groups. Purposefully, we have included suitable functional groups that have been converted to the targeted end products. All the reactions proceed very smoothly in moderate situations that provide the final products with good yields. The compounds are characterized by solubility, melting point, FTIR, and NMR. A notable strength of boronic acid molecules is their ability to be strategically incorporated into biologically active molecules, leading to improved selectivity, modified physicochemical properties, and enhanced pharmacokinetic behavior, which can elevate the overall therapeutic effect.

LIST OF FIGURES

Figure No.	Contents	Page No.
1.1	Characteristics of late-stage functionalization	2
1.2	Late-stage functionalization of drug candidates	3
1.3	Peptide chain modification via late-stage functionalization	4
1.4	Examples of silicon isosteres of carbon	8
1.5	Organoboron compounds	11
1.6	Applications of boronic acid derivatives in biology and their activities	12
1.7	Bortezomib, Ixazomib, Vaborbactam	12
2.1	Silicon incorporation in linezolid	13
2.2	Silicon incorporation in Campothecin	14
2.3	Estrogenic activity of phenols.	15
2.4	C/Si bioisosterism in muscarinic antagonists	16
2.5	Antiviral activity of silaspirane amines	16
2.6	Silicon-substituted oxadiazoles showing antiallergic activities	17
2.7	Some of the *sila* amino acids	17
2.8	Silicon analogs of pregabalin	18
2.9	Silicon-incorporated α, β, and γ amino acids	19
2.10	More examples of organosilanes	19
2.11	Compound SM23, an inhibitor of class C βlactamases.	25
2.13	BPBA compound, is a disruptor of the Rev-RRE interaction and acts as an inhibitor of HIV-1 replication	26
2.14	Representative Examples of Benzoxaborole	27

LIST OF TABLES

Table No.	Contents	Page No.
1.1	The properties and potential benefits of silicon in medicinal chemistry	9
2.1	Biological activity of the derivatives of benzoxaboroles	29
3.1	Optimization Table	31
3.2	Synthesis of Selected Boronate derivatives	32

Table of contents

CHAPTER 1: INTRODUCTION 1

1.1 Late-Stage Functionalization 1

1.1.2 Applications of Late-stage functionalization 1

1.1.2.1 Late-stage functionalization in new drug discovery 1

1.1.2.2 Late-stage functionalization in Peptide Modification 2

1.2 Heterocyclic Compounds 3

1.3 Organosilicon Compounds 4

1.3.1 Silicon Switch 5

1.3.2 ADMET 6

1.3.3 Effects of silicon on medicinal chemistry 6

1.4 Organoboron compounds 8

1.4.1 Impact of boron on medicinal chemistry 9

1.4.2 Drugs containing boronic acid 10

1.4.2.1 Boratezomib, Ixazomib and Vaborbactam 10

CHAPTER 2: LITERATURE BACKGROUND AND RESEARCH OBJECTIVE 11

2.1 Incorporation of Si in Drug Discovery 11

2.1.1. Silicon Incorporation to Increase Brain Penetration 11

2.1.2 Silicon Analogs of Campothecin 12

2.1.3 Hydrogen Bonding Capability of Silanols 13

2.1.4 Lipophilicity of silicon increases the cellular penetration 13

2.1.5 Muscarinic antagonists C/Si bioisosterism 13

2.1.6 Antiviral and antiallergic activity 14

2.1.7 Silicon-Containing Amino Acids 15

2.1.7.1 Silicon analogs of pregabalin 16

2.1.7.2 Silicon-incorporated α, β, and γ amino acids.....16

2.1.8 Examples for organosilanes that have started clinical trials [20] 17

2.1.9 Conversion of Aryl Benzyl Ethers into Oxametallacycles and 2-Phenyl-3-Substituted Benzo[b]furan 17

2.1.5 Challenges of Incorporating silicon 18

2.2 Importance of Organoboron Compounds in Drug Discovery.....19

2.2.1 Synthetic processes to obtain aryl boronic acids 19

b) Coupling of aryl halides with diboronic acid reagents [32], [34].....19

2.2.2 SERD boronic acid analogue based on the drug Fulvestrant.....20

2.2.3 Camptothecin prodrug with boronic acid moiety 21

2.2.4 Boronic acid autotaxin inhibitor 22

2.2.5 Compound SM23, an inhibitor of class C β-lactamases 23

2.2.6 Antiviral Activity 24

2.2.7 Benzoxaboroles.....25

Research objectives.....27

CHAPTER 3: RESULTS AND DISCUSSION, REACTION MECHANISMS, CONCLUSION AND EXPERIMENTAL PROTOCOLS.....28

3.2 Synthesis of 6-Amino-1-hydroxy-2,1-benzoxaborolane 33

Scheme: Synthesis of 6-Amino-1-hydroxy-2,1-benzoxaborolane.....33

3.3 Synthesis Of Oxasilacycles by Silicon incorporation in THF moieties;.....34

3.2.1 Experimental Procedures 36

3.2.1.1 General procedure 1: Synthesis of (4-(benzylcarbamoyl)phenyl)boronic acid from 4-carboxyphenylboronic acid (Scheme 3.1 and 3.2) 36

3.2.1.2 Synthesis of corresponding carbamoylphenyl boronic acid from 2-Aminophenol (scheme 3.4).....36

3.2.1.3 Esterification of Amino acids (Scheme 3.5) 37

3.2.1.4 Reduction of 3-nitro-5-((1-phenylethyl) carbamoyl)phenyl boronic acid to 3-amino-5-((1-phenylethyl)carbamoyl) phenylboronic acid (Scheme 3.9) 37

CHAPTER 4: EXPERIMENTAL DATA AND REFERENCES 40

4.1 Experimental Data 40

4.1.2 Synthesis of (4-((6-hydroxycyclohexa-1,5-dien-1-yl)carbamoyl)phenyl) boronic acid.....42

REFERENCES: 47

CHAPTER 1: INTRODUCTION

1.1 Late-Stage Functionalization

Late-stage functionalization (LSF) is an innovative technique in organic chemistry that allows complicated compounds, such advanced drug candidates or natural products, to be directly modified at the end of synthesis. This method enables quick molecular property diversification and optimization by enabling scientists to add additional functional groups without the requirement for time-consuming de novo synthesis [3]. In drug discovery, LSF is especially useful because it facilitates the rapid investigation of structure-activity correlations (SAR) and improves the pharmacokinetic and pharmacodynamic characteristics of lead compounds. LSF facilitates the effective synthesis of analogues by utilizing chemoselective processes that can withstand a broad range of functional groups, which speeds up the drug development process [4]. In summary, late-stage functionalization stands as a powerful tool in modern synthetic chemistry, offering efficient pathways to modify complex molecules and streamline the development of new therapeutics.

1.1.2 Applications of Late-stage functionalization

1.1.2.1 Late-stage functionalization in new drug discovery

The most advantageous techniques for drug discovery in contemporary drug development, late-stage functionalization (LSF) has become a transformative technique that allows for the direct modification of intricate, physiologically active compounds at later stages of synthesis. By enabling the quick creation of structural analogues without requiring total resynthesis, this method speeds up lead optimization and structure–activity relationship (SAR) research. By adding functional groups like hydroxyl, halogen, or amine moieties to drug-like scaffolds, LSF can greatly improve potency, selectivity, and pharmacokinetic characteristics. Although site selectivity and functional group tolerance present difficulties, ongoing developments in catalysis and reaction design are expanding the use of LSF and making it a crucial instrument for the creation of next-generation medicines. Innovative chemical synthesis is still a major obstacle in drug development efforts, even with the quick advances in academic research [9]. LSF has consequently emerged as a key approach in drug discovery, and the toolset accessible to medicinal

chemists has been significantly increased by reactions that support LSF. Researchers can forecast and regulate the site selectivity of LSF on drug-like targets by utilizing a variety of response patterns. The reaction manifolds of these potent instruments can be used to classify them [5].

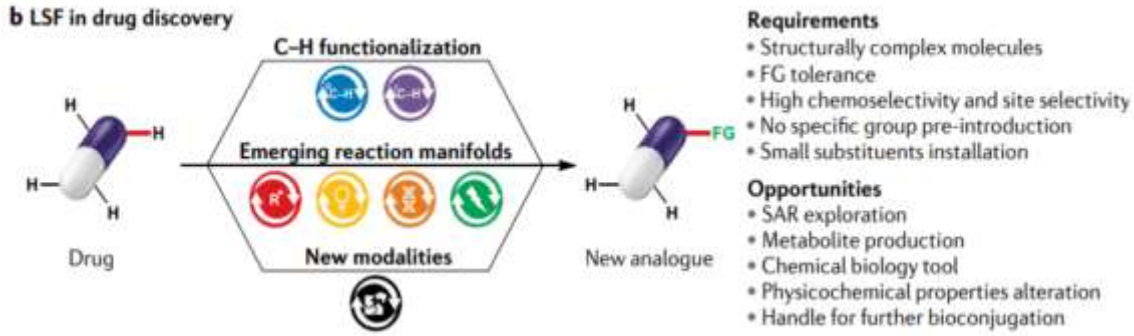


Figure 1.2: Late-stage functionalization of drug molecule

1.1.2.2 Late-stage functionalization in Peptide Modification

In peptide modification, late-stage functionalization (LSF) is a potent technique that enables chemical modifications to be made to fully or almost complete peptides without re-synthesizing the entire molecule. This method is frequently employed to enhance pharmacological characteristics like biological activity, solubility, and stability. Common LSF techniques include side-chain modifications of amino acids like cysteine and lysine, bio-orthogonal processes like click chemistry, and C–H activation (frequently with transition metals). High selectivity and functional group tolerance are provided by emerging methods that additionally use photochemical, electrochemical, and enzymatic processes. Rapid analogue generation, peptide–drug conjugates, and site-specific labeling for imaging or diagnostics are all made possible by LSF, which is very useful in drug discovery. Although there are still obstacles to overcome, like maintaining peptide activity and attaining site-selectivity.

Through C-H activation, this novel approach enables the creation of new C-C and C-X bonds, including arylation, alkynylation, fluorination, hydroxylation, and azidation, and permits the selective functionalization of non-polar amino acids within peptides (see Figure 4). Significant advancements have been made in the modification of lengthy peptides, especially those that contain tryptophan, without the use of protecting groups,

using C-H arylation and alkynylation techniques catalyzed by palladium (Pd) or gold (Au). The creation of a novel biaryl stapling method for complex peptides, the introduction of 18F radiofluorine, and various post-synthetic applications on bioactive cyclopeptides like valinomycin and aureobasidin are other noteworthy accomplishments that highlight the enormous potential of late-stage C-H activation reactions in peptide-based therapeutics [7].

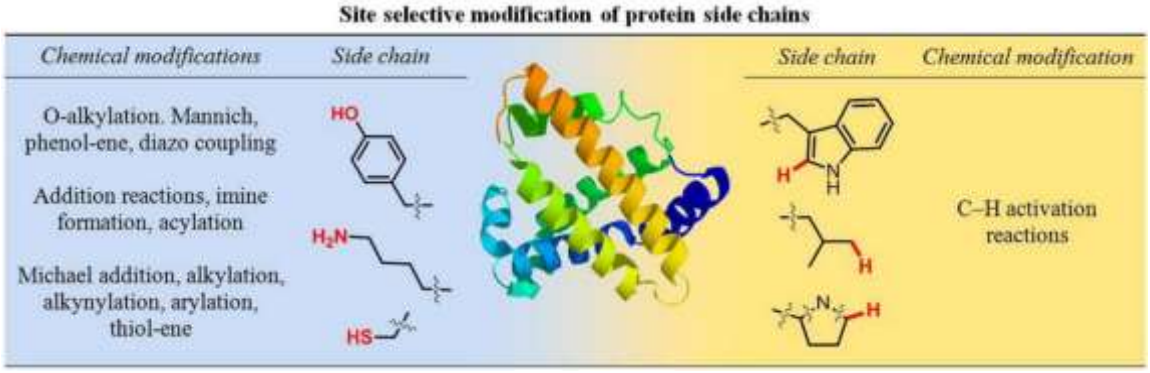
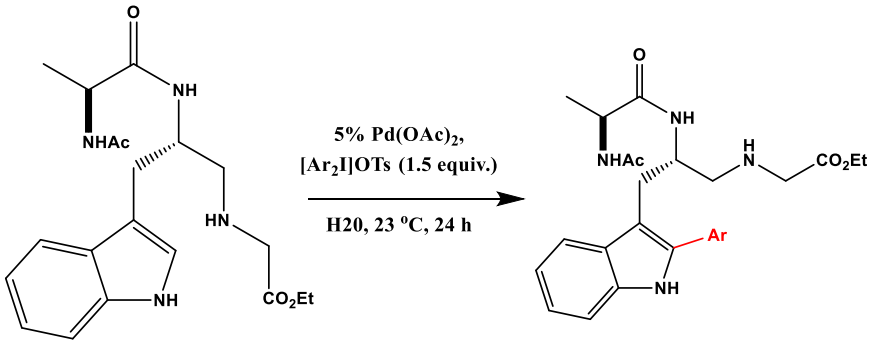


Figure 1.3: Peptide chain modification *via* late-stage functionalization



Scheme 1.1: Peptide modification *via* late-stage functionalization

1.2 Heterocyclic Compounds

Heterocyclic molecules are characterized by a ring structure that includes at least one atom that is not carbon, Nitrogen (N), oxygen (O), and sulfur (S) are the most usual heteroatoms in these rings, while silicon, phosphorus, and boron can also be included, though less commonly. The electrical distribution, reactivity, and general chemical behavior of these compounds are significantly impacted by the presence of heteroatoms. Heterocycles are therefore essential in many branches of chemistry, including medicinal chemistry and organic synthesis. In order to successfully interact with enzymes, receptors, and nucleic acids and display a broad spectrum of biological functions, heterocyclic

scaffolds frequently imitate the structure and function of biological molecules.Because of their structural diversity and functional adaptability, these compounds serve as the structural foundation of many pharmacological medications. For example: A fused heterocyclic system is included in the stimulant caffeine. The β-lactam ring, a nitrogen-containing four-membered heterocycle, is a characteristic of the commonly used antibiotic penicillin. Heterocyclic structures are also found in other significant medications, such as azithromycin, pyrimethamine, morphine, and chlorpromazine. Furthermore, the development of anti-inflammatory, antiviral, antimalarial, antihypertensive, and anticancer drugs heavily relies on heterocycles. Heterocyclic compounds are crucial for agrochemicals, dyes, polymers, and materials research in addition to pharmaceuticals. In conclusion, heterocyclic molecules are essential to contemporary chemistry. They are the building blocks of innumerable medications and therapeutic agents, and further research into them is essential to the creation of novel cures for a wide range of illnesses.

1.3 Organosilicon Compounds

Silicon comes directly below carbon in the third row of the periodic table, which has the atomic number 14. It makes up around 25% of the total earth's crust and is the second most prevalent element there [15].It is generally believed that there are no naturally occurring organosilicon compounds, that is, compounds with at least one Si-C bond and that it is never found in its elemental form. Instead, it only exists in combination with other elements, primarily oxygen [16]. Although they can both form tetrahedral compounds and have a valency of 4, silicon and carbon differ greatly in their characteristics.

Since carbon has a rich and distinct chemistry and is regarded as the element of life, a whole field of chemistry called "organic chemistry" dedicates itself to studying carbon molecules. Catenation, the ability of carbon to make stable bonds with itself, is what gives rise to this diversity in carbon compounds. The Si−O bond (368 kJ mol−1) is stronger than the Si−Si σ (sigma) bond (230 kJ mol−1), and silicon does not form stable π (pi) bonds [17]. Silicon is mostly found in nature as silicates and silica because of the Si-O bond's increased stability. The molecule adopts the alternate pathway due to the intrinsic stability of the Si−O bond and the instability of the Si=C bond.

Organosilicon chemistry is a rapidly expanding field. Methods appropriate to the production of scaffolds containing silicon are given particular attention. Recent advances

in fields like electrochemistry, C-H bond activation, cross- coupling reactions, hydrosilylations, carbosilylations, the creation of silicon stereogenic compounds, silicon-containing small rings, the synthesis of silanols, and numerous other synthetic procedures[6].

1.3.1 Silicon Switch

Silicon and carbon frequently considered to be being similar, an isostere of sp3 hybridized carbon with silicon. In many instances, there is a clear dichotomy also exists between silicon and carbon, and these variations frequently result in physiochemical and biological profile that are markedly different. Because of the incorporation of silicon center in the organic compounds the outcome of the same drug become more efficient. This domain of drug development gained a lot of interest and expanded quickly in the last ten years[7],[8].

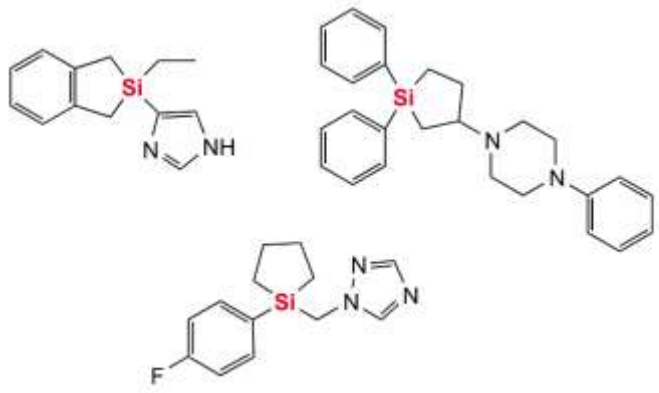


Figure 1.4: Examples of silicon isosteres of carbon

In the 1970s, Tacke and coworkers proposed the idea of incorporating a "silicon switch,"[8] or more precisely, a silicon-carbon substitution, to create new bioactive candidates. With this approach, a compound could be altered by substituting silicon atoms (or functional/structural groups containing silicon atoms) for one or more carbon atoms. A silicon switch of this kind could be viewed as a traditional tetravalent bioisostere[9]. But the use of this strategy continues to be underappreciated and, as a result, frequently underutilized. Utilizing silicon as a carbon bioisostere in scaffolds that resemble drugs has garnered more attention recently.

1.3.2 ADMET

The design and development of novel and enhanced drug-like molecules for disease therapy need to have minimal toxicity, physiologically acceptable pharmacokinetics, good action, and selectivity. The medicinal chemist has historically uses an iterative design process to generate lead active pharmaceutical ingredients (APIs), balancing activity that deviates from the parameters like selectivity, solubility, absorption, distribution, metabolism, excretion, and toxicity (ADMET)[10].

Nowadays, when designing new biologically active compounds, drug developers frequently look to well-known drug families for inspiration. According to recent data, there are only about three dozen scaffolds that are regularly used, and they make up about half of all compounds that have received FDA approval. These same research have also demonstrated that a very modest number of distinct functional groups were used to construct the majority of the tiny bioactive molecule side-chains observed in current drug architectures.

These findings have also prompted the use of bioisosteres as a contemporary drug design technique, with the objective of using them to enhance the ADMET characteristics of small molecule drug-like entities or to produce new subclasses of compounds with altered properties.

1.3.3 Effects of silicon on medicinal chemistry

Four valence electrons are present in both silicon and carbon atoms. The physical and biochemical characteristics of silicon-containing analogues can differ significantly from those of their carbon-parent compounds due to some of these basic differences. Three primary factors determine silicon's usefulness in organic synthesis: its relative electronegativity, its bond strengths to other elements, and whether or not its valence p- and empty d-orbitals are involved.

Property	Difference	Potential benefit
Bonding	Altered bond strength and disfavoured multiple bonds	• Silane diol peptidomimetics • Access to bioisosteres not structurally available to carbon
Atomic size	Altered bond lengths and bond angles	• Altered in vitro potency • Modified selectivity • Altered rate of metabolism
Electronegativity	Increased H-bond strength and acidity of silanols	• Improved potency in pharmacophores where H-bonding is important
Lipophilicity	Increased lipophilicity of silicon-containing compounds	• Improved in vivo half-life • Enhanced tissue distribution • Enhanced cell penetration

Table 1.1. The properties and potential benefits of silicon in medicinal chemistry [11]

Silicon has a strong affinity for oxygen, forming more stable bonds with oxygen and halogens than with carbon. However, its bonds to carbon and hydrogen are weaker than their respective carbon bonds. Modern organosilicon synthetic chemistry focuses on creating stable silicon-oxygen and silicon-fluoride bonds while breaking weaker silicon bonds. The chemistry of silicon-carbon (Si–C) and silicon-oxygen (Si–O) single bonds is central to silicon's overall chemistry, supporting its role as a tetrahedral bioisostere of carbon. While some silicon-sigma (σ) bonds are strong, silicon-pi (π) bonds are generally weak [12], making stable sila-equivalents for alkenes and carbonyls rare, despite some isolated double bond compounds. Silicon also struggles to form stable silicon-hydrogen (Si–H) bonds, which are weaker and have reversed polarity compared to carbon-hydrogen (C–H) bonds. For instance, the Si–H bond can easily react with water, yielding silanol (Si–OH), whereas C–H bonds remain stable. These bonding differences allow for the synthesis of sila-analogues, where carbon counterparts might be difficult or impossible to obtain.

For instance, the C–C bond length is around 1.54 Å, whereas the C–Si bond length is approximately 1.87 Å [23]. Silicon-containing bonds are longer than their carbon counterparts. The trimethylsilyl (TMS) group serves as an example of this distinction;

despite its bigger size, it is less sterically demanding than the tert-butyl group. The size and shape of silicon-containing compounds differ from those made entirely of carbon due to the change in bond lengths, which also affects the pharmacological profiles and interactions of these silicon analogues with biological targets. Additionally, silicon's greater electropositivity makes carbon-silicon bonds more polarized, leading to differing polarities for bonds between silicon and other elements.

Compared to their carbon-based counterparts, molecules containing silicon are often more hydrophobic and lipophilic.[13] This increased lipophilicity can significantly enhance tissue penetration and lead to longer plasma half-lives, as these molecules are less susceptible to hepatic metabolism. Lipophilicity is also essential for small molecule drug candidates to get through the blood-brain barrier (BBB), with many computational models incorporating this criterion to predict BBB permeability. The computational research on small silicon-containing molecules has recently gained attention, with in silico studies often used to support the bonding characteristics of silicon atoms.

1.4 Organoboron compounds

Boron (B) is a chemical element with the atomic number 5. It constitutes approximately 0.001 percent of the Earth's crust by weight. It is classified as a metalloid, meaning it displays properties of both metals and nonmetals. In its crystalline form, boron is hard, brittle, and appears as a dark gray or black solid. Meanwhile, in its amorphous form, it exists as a brown powder. As a Lewis acid, boron is known for its ability to accept a pair of electrons. At room temperature, crystalline boron is nearly inert chemically. It is unaffected by boiling hydrochloric acid, and hot nitric acid is only slowly converted to boric acid (H_3BO_3).

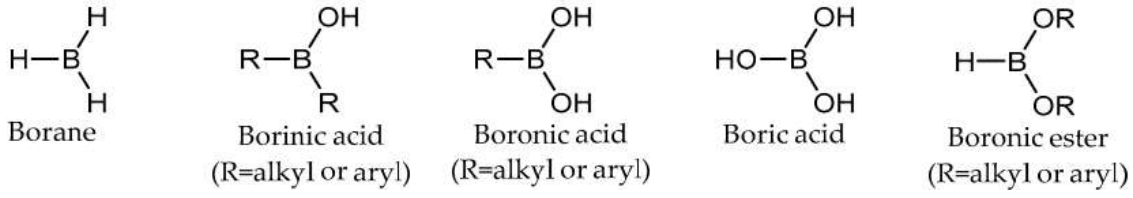


Figure 1.5 : Organoboron compounds

Although boron and carbon share some intriguing parallels, boron acids have distinct physicochemical and electrical properties. Additionally, boronic acids are regarded as carboxylic acid bioisosteres.

1.4.1 Impact of boron on medicinal chemistry

Boron is a relatively new element in drug design, and the biological activity of many boron-containing compounds has been documented over the past decade. In the past, medicinal chemistry largely overlooked boron-containing compounds because they were thought to be toxic. However, recent research has shown that these compounds are typically non-toxic, challenging the previous perception. The great significance of boronic acids in the synthesis of pharmaceutically active compounds and their applications are the major reasons. Among the boron containing compounds, boronic acid is the most studied in organic chemistry [1].

Boric acids, first synthesized by Edward Frankland in 1860 [14]. The simple synthesis and stability of the group have led to its application in various important synthetic reactions, including hydroboration (C–H, C–OH bonds)[15], Suzuki–Miyaura coupling (C–C bonds)[16], [17], and Chan–Lam coupling (C–N and C–O bonds)[18].

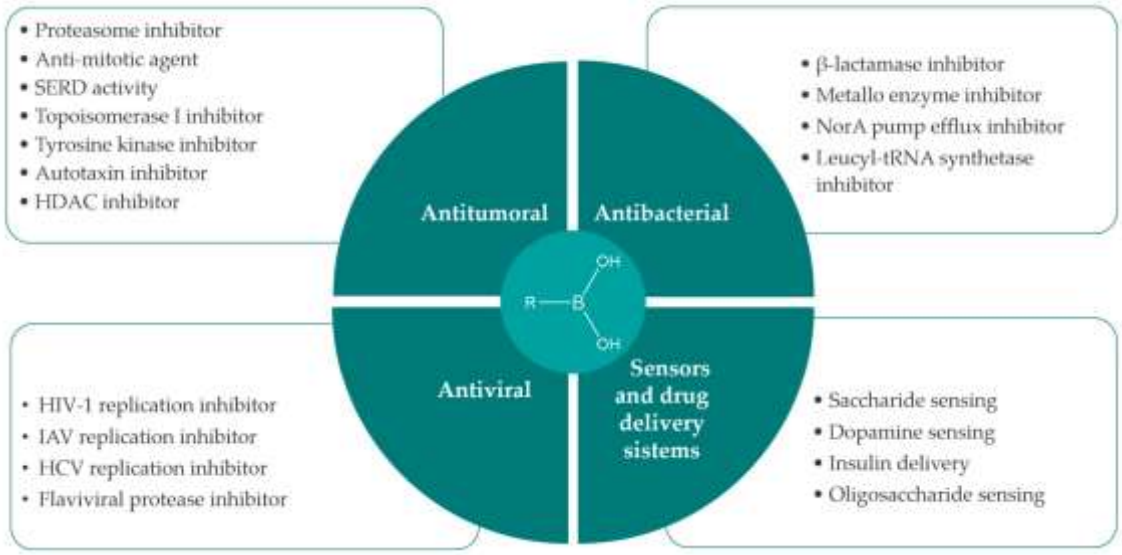


Figure 1.6: Applications of boronic acid derivatives in biology and their activities[2], [19]

1.4.2 Drugs containing boronic acid

1.4.2.1 Boratezomib, Ixazomib and Vaborbactam

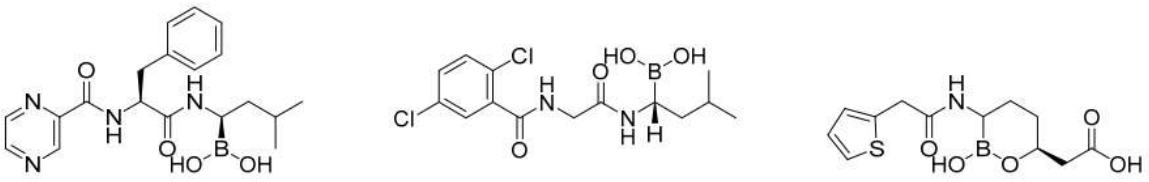


Figure 1.7: Boratezomib, Ixazomib, Vaborbactam

Bortezomib[1], also known as Velcade, was the first drug containing boronic acid to be licensed by the European Medicines Agency (EMA) in 2004 and the Food and Drug Administration (FDA) in 2003. It was used to treat multiple myeloma. Interest in boronic acids grew after it was approved [2], which prompted the creation of two other medications: Vaborbactam and Ixazomib. The FDA and EMA authorized Ixazomib in 2015 and 2016, and it is also used to treat multiple myeloma. The FDA and EMA approved Vaborbactam in 2017 and 2018, respectively. It works as a β-lactamase inhibitor and is used in conjunction with antibiotics to treat urinary tract, stomach, and lung infections.

CHAPTER 2: LITERATURE BACKGROUND AND RESEARCH OBJECTIVE

2.1 Incorporation of Si in Drug Discovery

2.1.1. Silicon Incorporation to Increase Brain Penetration

Reddy and his colleagues developed and studied silicon analogs of oxazolidinone antibiotics. Linezolid, the first oxazolidinone antibiotic to be marketed, is commonly used to treat infections. Currently, clinical trials are being conducted for sutezolid, a thiomorpholine derivative intended for tuberculosis treatment. They synthesized several compounds by substituting the oxygen or sulfur atoms in the oxazolidinone ring with silicon. The pharmacokinetics of the most effective substances demonstrated that the addition of silicon significantly increased the brain-to-plasma ratio. In comparison to linezolid, Siliconized Linezolids (where R = H and R1 = C(S)OMe, featuring a clogP of 5.55) exhibited a brain-to-plasma ratio that was 29 times higher. This substantial increase in central nervous system (CNS) exposure is attributed to the enhanced lipophilicity of these compounds.

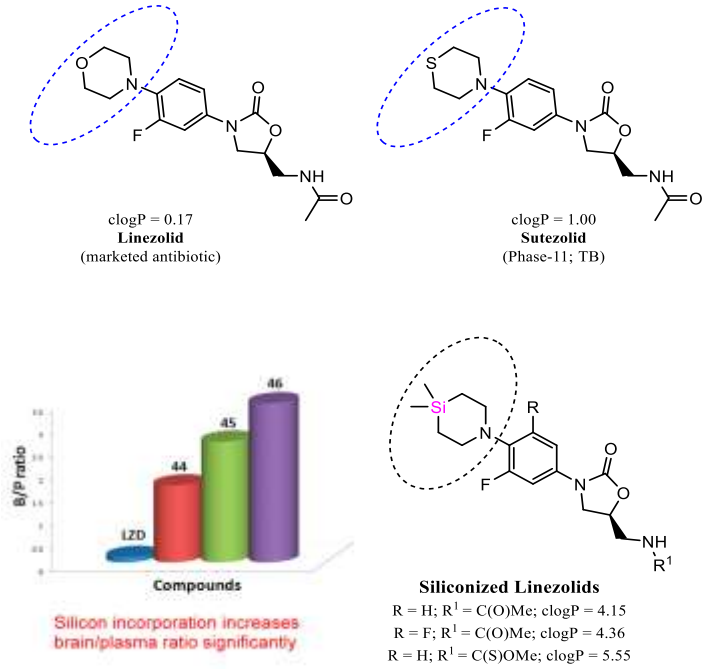


Figure 2.1: Silicon incorporation in linezolid[20]

2.1.2 Silicon Analogs of Campothecin

The synthesis of stable Camptothecin analogs has been enhanced by the increased lipophilicity of certain compounds through the structural addition of silicon. Camptothecin, a natural compound known for its anticancer properties, primarily exerts its effects by inhibiting the enzyme DNA topoisomerase I. In vivo, the hydrolysis of the δ-lactone moiety of Camptothecin can occur, with the lactone form of the drug being the active form that easily enters cells. The remarkable adherence of camptothecin's carboxylate group to albumin in human serum facilitates lactone hydrolysis and helps maintain concentration balance. A rise in lipophilicity causes a greater partitioning of compounds into the RBC, which in turn reduces the lactone hydrolysis. Numerous silicon analogues of Camptothecin, such as Karenitecin and DB-67 [21], [22], [23], [24], have been synthesized and assessed in clinical trials for the treatment of cancer in humans. Additionally, another related compound, DB-91 has demonstrated the capacity to cross the blood-brain barrier., leading to its testing for cancers that affect the central nervous system.

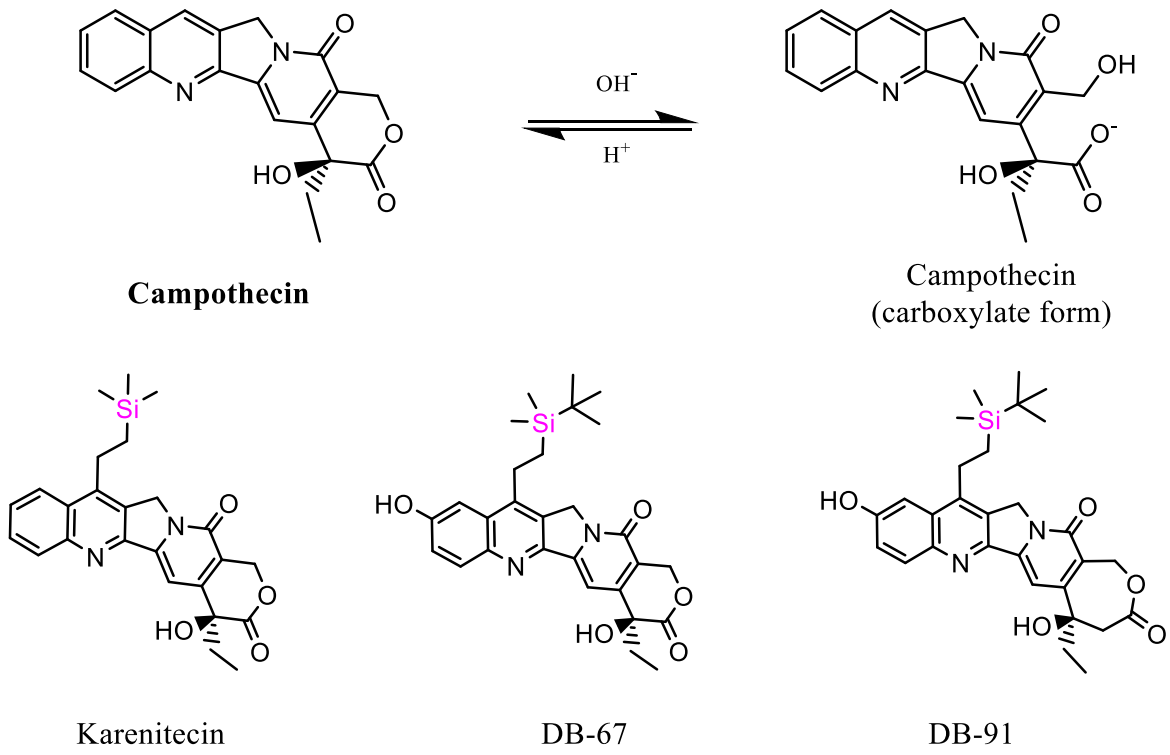


Figure 2.2: Silicon incorporation in Campothecin

2.1.3 Hydrogen Bonding Capability of Silanols

The p orbitals of oxygen and the empty 3d orbitals of silicon form a π bonding. silanols have a higher hydrogen bonding capacity and acidity than their corresponding carbinol. This property can be helpful in pharmacophores that mainly rely on hydrogen bonding interactions. The addition of silicon enhances antibacterial properties in a range of hydroxyl substances.

2.1.4 Lipophilicity of silicon increases the cellular penetration

In contrast to their carbon equivalents, lipophilic analogs of silicon have better cell penetration, which may boost the potency of certain drugs. And features like bond polarization, increased bond length, and conformational modifications may also cause to an increase in potency[25].

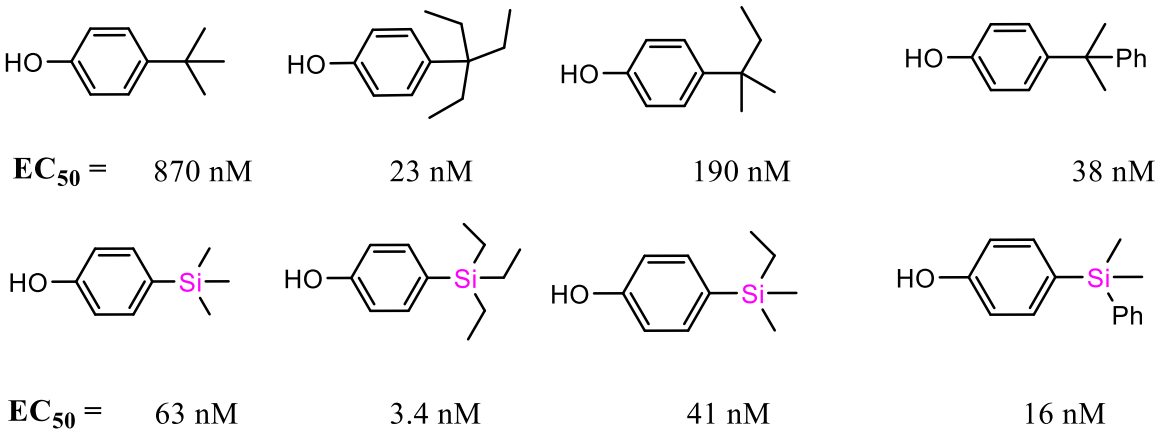


Figure 2.3: Estrogenic activity of phenols.

2.1.5 Muscarinic antagonists C/Si bioisosterism

Tacke looked into how muscarinic antagonists were affected by C/Si bioisosterism, muscarinic acetylcholine receptors, activated by acetylcholine, are antagonized to treat Parkinson's disease[25].

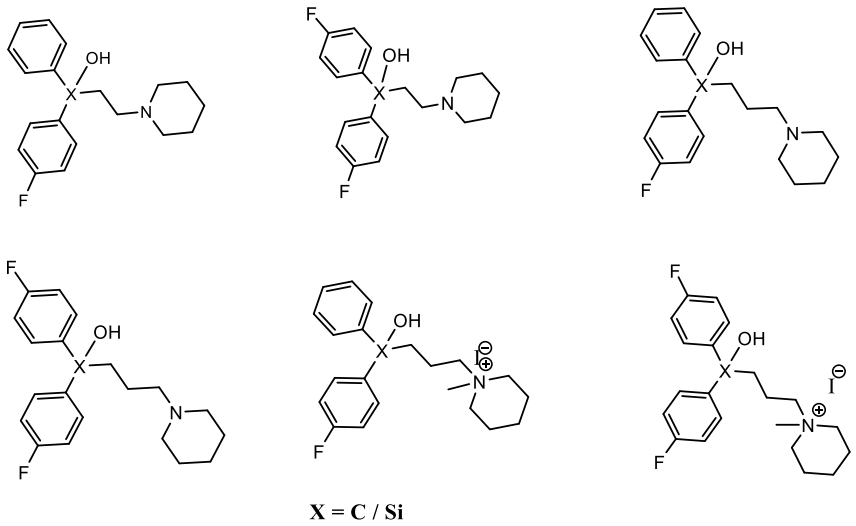


Figure 2.4: C/Si bioisosterism in muscarinic antagonists

2.1.6 Antiviral and antiallergic activity

DeGrado and colleagues reported on organosilylamine inhibitors of the M2 protein in influenza A. They discovered that increased lipophilicity enhances the strength of M2 inhibitors because of the protein's hydrophobic binding pocket. The researchers synthesized spirane amines and evaluated their activity against the A/M2-V27A variant. Their findings indicated that theIn comparison to their carbon-based counterparts, silicon analogs were more effective.[26]

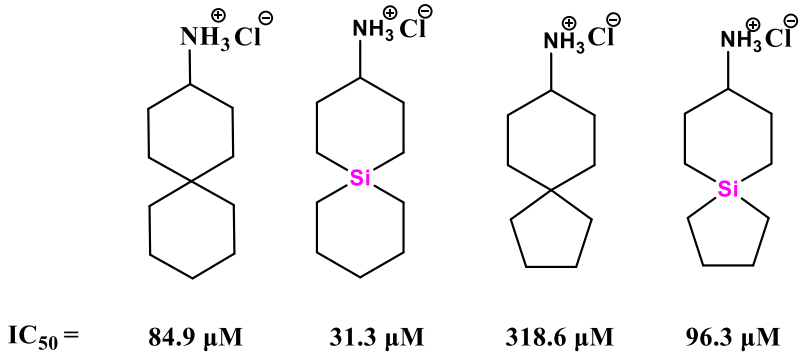


Figure 2.5: Antiviral activity of silaspirane amines

Meanwhile, Lee and colleagues examined the antiallergic properties of oxadiazoles modified with silicon. In the RBL-2H3 in vitro model, they discovered that the silicon-containing molecule was more effective than the comparable carbon derivative.[27].

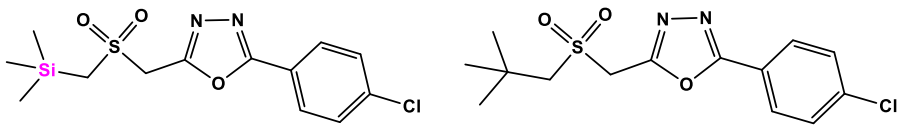


Figure 2.6: Silicon-substituted oxadiazoles showing antiallergic activities

2.1.7 Silicon-Containing Amino Acids

Unnatural α-amino acids are crucial molecules used across various applications, such as synthesizing modified peptides that enhance resistance to enzyme degradation and improve the characteristics of bioactive peptides. In particular, silicon-containing unnatural amino acids are gaining attention as notable building blocks. Peptides incorporating silyl amino acids show promise in maintaining biological activity while increasing resistance to degradation. As the pharmaceutical industry shows growing interest in silicon-containing amino acids and peptides, as well as medicines based on proteins and peptides is also on the rise. Non-proteinogenic amino acids, known as unnatural amino acids, can be created by chemists or obtained from nature. Examples of these are β-amino acids, D-amino acids, N-methylamino acids, and α-amino acids with altered side chains.[28]. These amino acids are frequently utilized in modified peptide synthesis because they evade recognition by proteolytic enzymes, thus enhancing peptides' resistance to biodegradation. Amino acids that contain silicon are especially desirable because they may be incorporated into bioactive substances like peptides., allowing for structural modifications that enhance lipophilicity. By integrating a lipophilic silicon moiety, it is possible to improve cell penetration and increase peptide stability against biodegradation. A comprehensive study of silicon amino acids was done by the Cavelier group, highlighting their importance in this field.

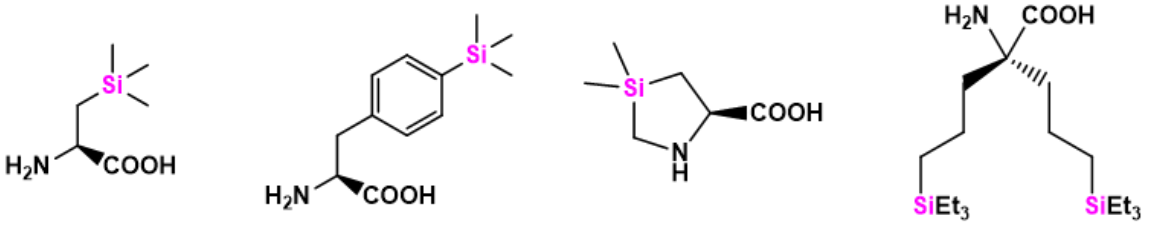


Figure 2.7: Representative sila amino acids

2.1.7.1 Silicon analogs of pregabalin

Silicon analogs of pregabalin, an analog of γ-aminobutyric acid (GABA), were synthesized by Marutake et al. used for treating epilepsy and neuropathic pain. In models of spinal nerve ligation, the antiallodynic activity of compounds silicon containing pregabalin was assessed, revealing that compound Silagaba compound had activity comparable to pregabalin. However, neither analog exhibited pregabalin's anticonvulsant effects or the associated adverse consequences include hypalgesia and dizziness[29]. According to these findings, silicon analogs of pregabalin may offer a similar therapeutic benefit with fewer central nervous system side effects.

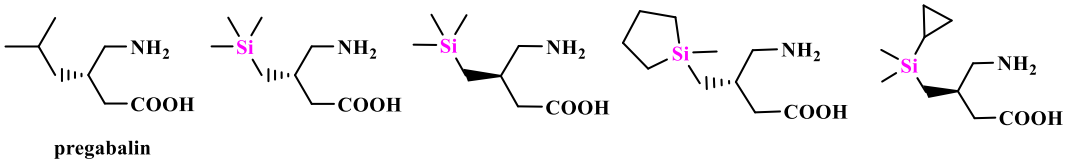


Figure 2.8: Silicon analogs of pregabalin

2.1.7.2 Silicon-incorporated α, β, and γ amino acids

Reddy and associates produced α, β, and γ amino acids with silicon incorporation, emphasizing the special 5,5-trans fusion from allylsilanes. This structure benefits from the longer C−Si bond compared to C−C bonds. The synthesis of the lipophilic sila-GABA derivative [30] is noteworthy as conformationally rigid GABA analogs are effective in treating various CNS disorders. This derivative is similar to the clinical candidate atagabalin and the antiepileptic medication gabapentin. with its 5,5-trans fusion mirroring the methyl group orientation seen in atagabalin.

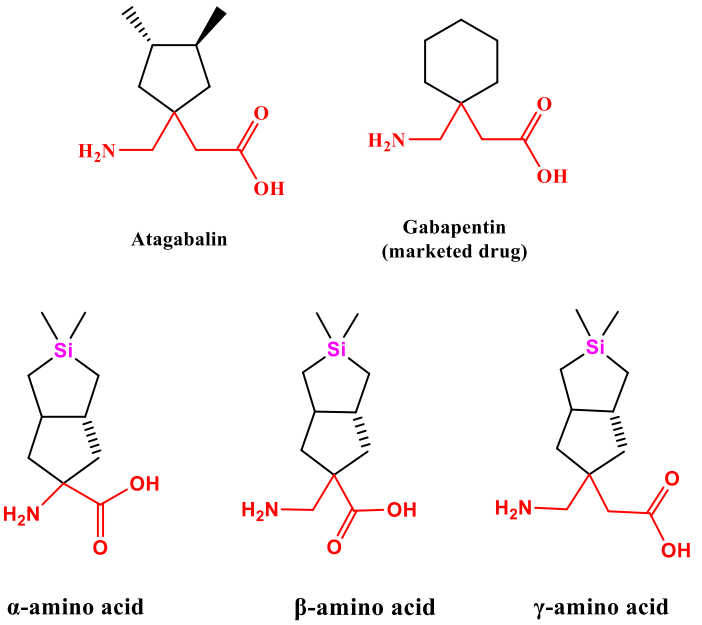
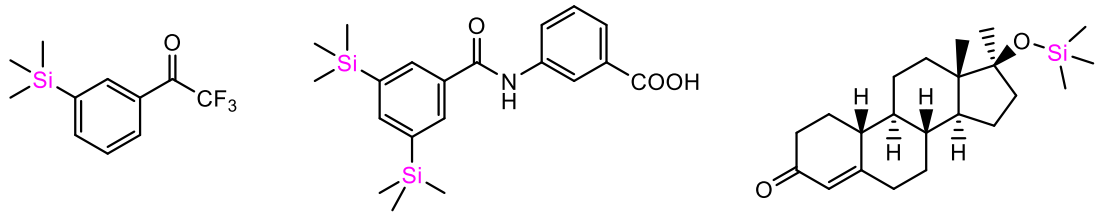


Figure 2.9: Silicon-incorporated α, β, and γ amino acids

2.1.8 Examples for organosilanes that have started clinical trials [20]



Zifrosilone/ MDL-73745
Alzheimer's disease and cognitive disorders (Phase II discontinued)

Amsilarotene/ TAC-101
Hepatocellular carcinomaretinoic acid receptor antagonist (Phase II discontinued)

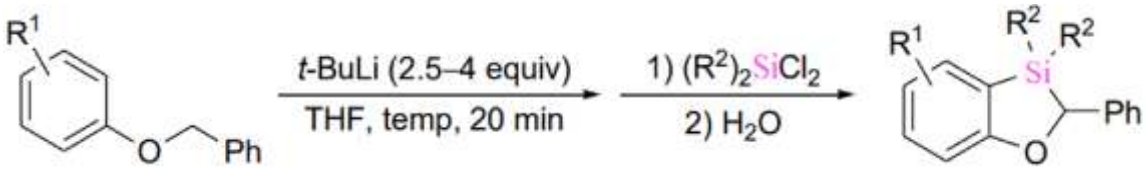
Silabolin
Cachexia
Anabolic and androgenic effects for multiple indications(Limited clinical trials)

Figure 2.10: More examples of organosilanes

2.1.9 Conversion of Aryl Benzyl Ethers into Oxametallacycles and 2-Phenyl-3-Substituted Benzo[b]furan

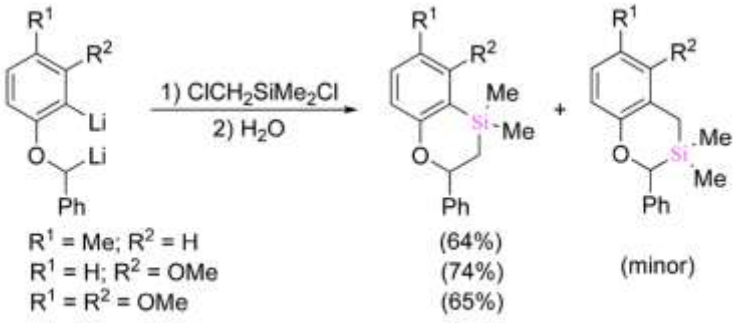
At low temperatures, aryl benzyl ethers undergo α-lithiation with t-BuLi to produce the α-lithiobenzyloxy group facilitates access to o-lithiophenyl α-lithiobenzyl ethers by acting as a directed metalation group (DMG). Methoxy groups at the meta location increase this ortho-directing effect. The resulting dianions can react with various electrophiles, such as carboxylic esters and dihalosilanes or germanes, producing compounds like benzofurans, sila(germa)dihydrobenzofurans, and silach roman

derivatives from aryl benzyl ethers. The researchers investigated oxygen heterocyclic derivatives by utilizing the 1,4-relationship of dianions 4 and reacting them with bis-electrophilic reagents. They selected Si and Ge dichlorides as electrophiles, producing moderate to high yields of sila and germadihydrobenzofurans., with functionalization reflected from the original aryl benzyl ethers. Furthermore, the reaction with carboxylic esters generated benzo[b]furan derivatives after acidic hydrolysis, achieving moderate to high yields with both heteroaromatic and aliphatic esters.



Scheme 2.1: Reactions of Selected Dianions with Me_2SiCl_2

3-tert-butylphenylbenzyl ether was used to evaluate the steric effect of a big alkyl group at a meta location; this resulted in perfect regioselectivity for o-lithiation at the less crowded ortho position. Wittig's rearrangement was also a little competitive. Furthermore, the dianions were stabilized by the combined action of the alkoxy and α-lithiobenzyloxy groups.leading to a lower base requirement for dilithiation of ethers. Consequently, various difunctionalized benzyl 3-methoxyaryl ethers, oxasilacycles, and benzofurans were synthesized efficiently with high yields[31].



Scheme 2.1: $ClCH_2SiMe_2Cl$ Reactions with Specific Dianions

2.1.5 Challenges of Incorporating silicon

Although adding silicon to drug-like scaffolds has many benefits, there are drawbacks as well. It is crucial to design effective synthetic pathways for compounds containing silicon

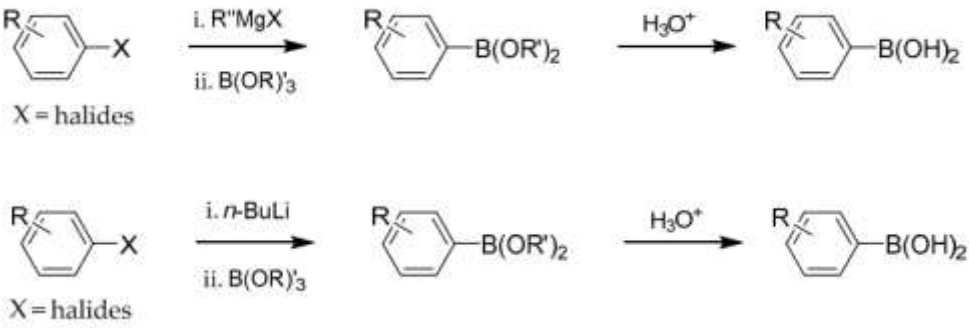
because problems with starting material availability and cost frequently occur. Moreover, structural differences in organosilanes are restricted by the intrinsic instability of bonds such as Si-H and Si-X. Pharmaceutical corporations may therefore be reluctant to investigate this field since they perceive the creation of novel scaffolds as more hazardous. While greater lipophilicity can boost potency, it may also weaken the molecule's ability to function as a medication.

2.2 Importance of Organoboron Compounds in Drug Discovery

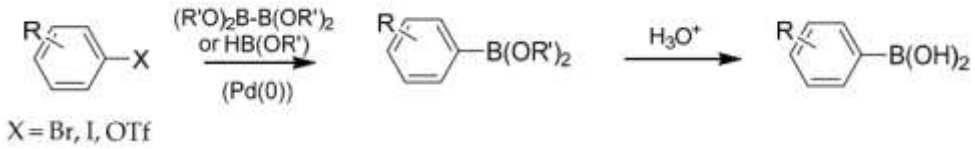
The atomic number of the chemical element boron (B) is **5**. By weight, it makes up about 0.001 percent of the Earth's crust. Because it exhibits characteristics of both metals and nonmetals, it is categorized as a metalloid. When crystalline, boron is a dark gray or black solid that is hard and brittle. In contrast, it exists as a brown powder in its amorphous state. The ability of boron to take up two electrons is what makes it a Lewis acid. At room temperature, crystalline boron is nearly inert chemically. It is unaffected by boiling hydrochloric acid, and finely ground boron is only slowly converted to boric acid (H_3BO_3) by hot concentrated nitric acid.

2.2.1 Synthetic processes to obtain aryl boronic acids

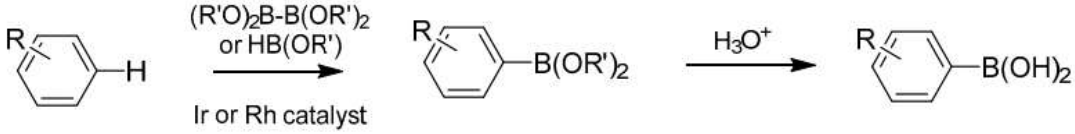
a) Electrophilic trapping of arylmetal intermediates with borate esters from aryl halides make use of Grignard reagents [32] or through Li- H exchange [33], respectively.



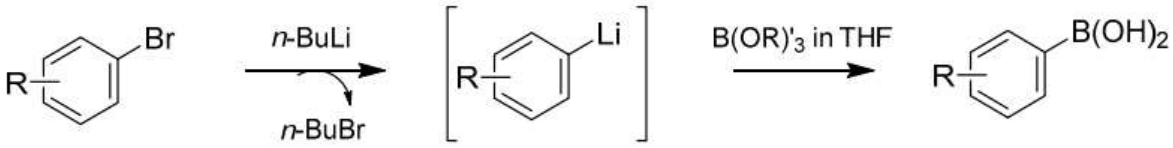
b) Coupling of aryl halides with diboronic acid reagents [32], [34]**.**



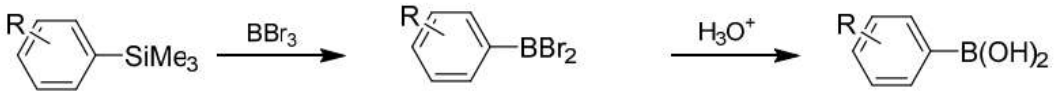
c) Direct boronylation by transition metal-catalyzed aromatic C–H functionalization [35], [36].



d) Bromide–lithium exchange reaction through flow chemistry [37]



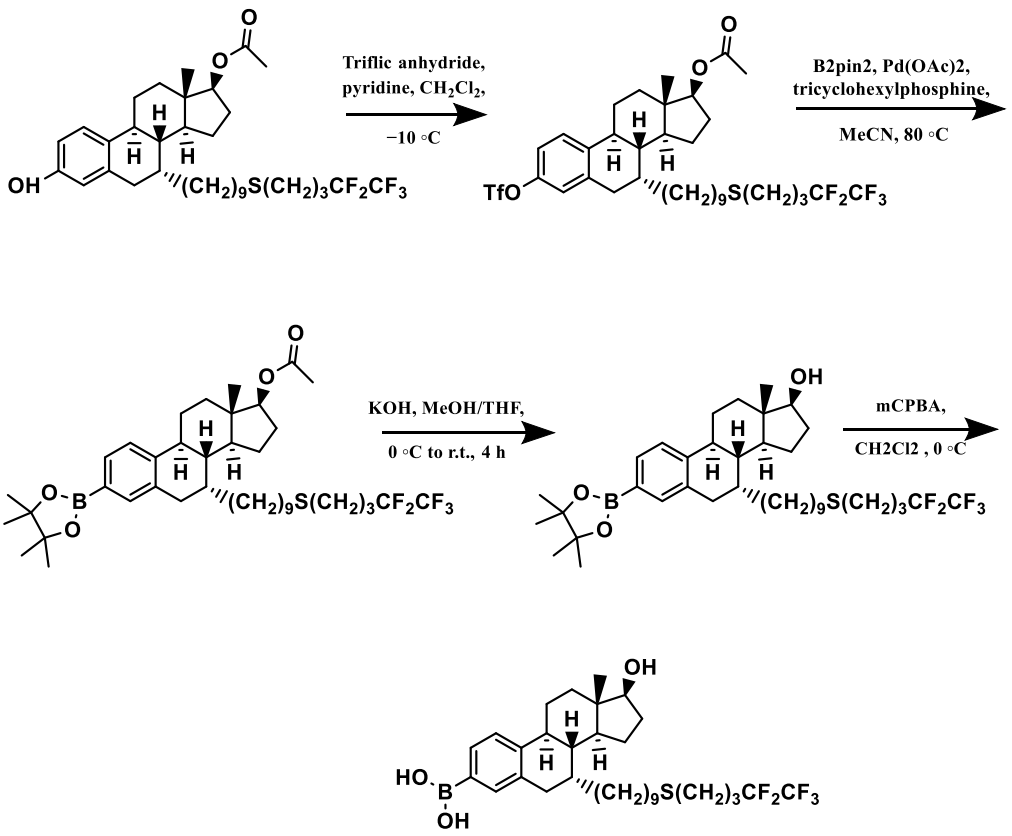
d) Transmetallation of aryl silanes and stannanes [32], [38].



Scheme 2.11: Synthetic processes to obtain aryl boronic acids

2.2.2 SERD boronic acid analogue based on the drug Fulvestrant

Fulvestrant was converted into a boronic acid derivative to increase its oral bioavailability and removes the requirement for intramuscular injection. Fulvestrant is a selective estrogen receptor down-regulator (SERD) that binds to estrogen receptor α (ERα) to treat estrogen receptor-positive (ER+) metastatic breast cancer. By substituting a boronic acid for the 3-OH group, the change greatly decreased first-pass metabolism and improved bioavailability while preserving pharmacological characteristics. Derivatives of boric acid are believed to reduce first-pass metabolism by attaching to sugar molecules and glycoproteins and stopping glucuronidation. Furthermore, SERD boronic acid analogue, ie, final product effects on inhibiting cell proliferation in different breast cancer cell lines were similar [39].



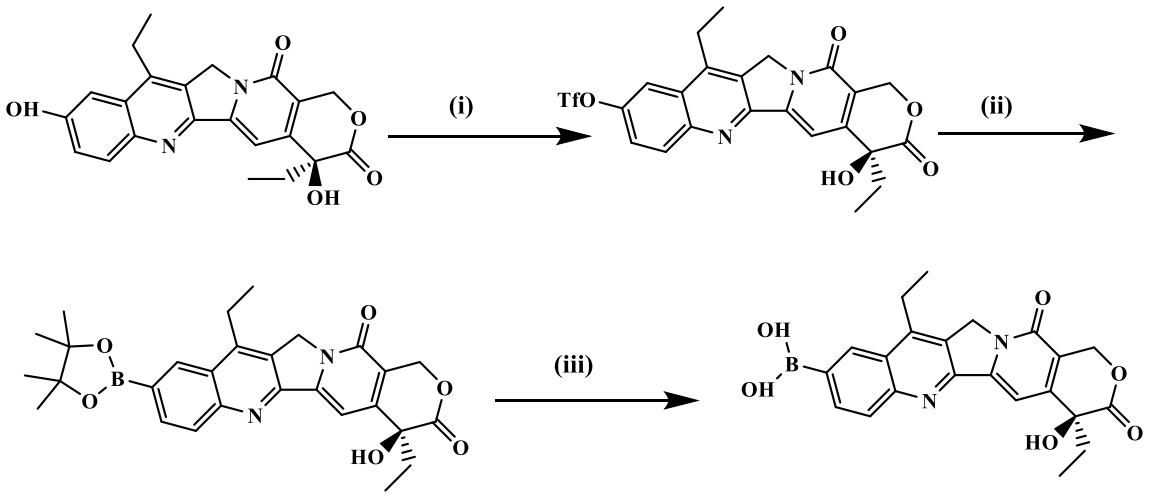
Scheme 2.12: SERD boronic acid analogue based on the drug fulvestrant

Table 4. Effects on growth inhibition (IC_{50}, μM) of fulvestrant and compound **43** in different breast cancer cell lines.

Compound	MCF-7	T47D
Fulvestrant	0.0015	0.0012
43	0.0032	0.0061

2.2.3 Camptothecin prodrug with boronic acid moiety

A boronic acid prodrug known as 7-ethyl-10-boronic acid (final compound) was used to develop a method for the selective release of Camptothecin, an anticancer compound that inhibits the enzyme topoisomerase I and causes cell death. This prodrug takes advantage of hydrogen peroxide's (H2O2) ability to oxidize boronic acids, which is more prevalent in cancer cells than in healthy cells. Furthermore, the polysaccharide glycocalyx on the surface of cancer cells can be bound by boronic acids to form boronate esters, which improve drug selectivity. It is possible to the selectively release camptothecin directly to cancer cells by oxidizing 10-boronic acid to 10-OH with H2O2 [51].

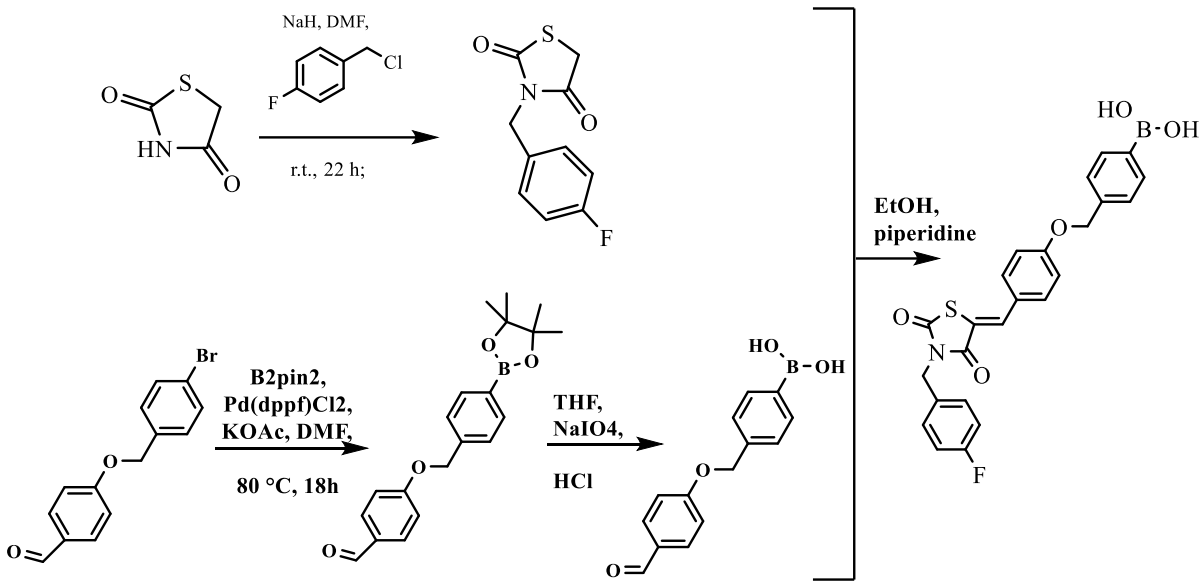


Scheme 2.13: Synthesis of Camptothecin prodrug with boronic acid moiety

Reaction conditions (**i**) N,N-bis(trifluoromethylsulfonyl)aniline, triethylamine (TEA), DMF, 60 ˚C, 3 h; (**ii**) [1,10-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($Pd(dppf)Cl_2$), KOAc, B_2pin2 , 1,4-dioxane, 80 ˚C, 12 h; (**iii**) $NaIO_4$, NH_4OAc, 1:1 C_3H_6O:H2O, r.t., 24hrs.

2.2.4 Boronic acid autotaxin inhibitor

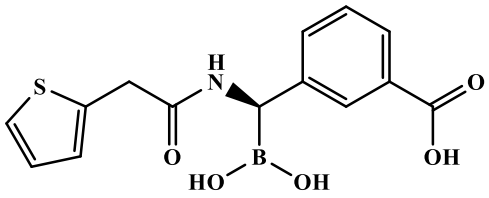
A convergent technique (scheme) was used to manufacture 4-((4-((3-(4-fluorobenzyl)-2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)methyl) phenylboronic acid. The Suzuki–Miyaura reaction was used to synthesis the boronic acid, while the thiazolane-2,4-dione and diphenyl boronic acid were created independently. To create 4-((4-((3-(4-fluorobenzyl)-2,4-dioxothiazolidin-5-ylidene)methyl) phenoxy)methyl)phenyl boronic acid, these moieties were then joined via a Knoevenagel condensation [52].



Scheme 2.14: Boronic acid autotaxin inhibitor

2.2.5 Compound SM23, an inhibitor of class C β-lactamases

Compound SM23 is a studied boronic acid β-lactamase inhibitor, classified as a boronic acid β-lactamase inhibitor (BATSI) and noted as most effective inhibitors of class C β-lactamases. It was designed using a mimetic approach, where various chemical groups surround a boronic acid to mimic the natural β-lactam substrate. Structure-activity relationship (SAR) studies indicate that adding a negatively charged group, like a carboxylate, enhances binding affinity and cell penetration. Furthermore, a hydroxyl group of the boronic acid is essential for interaction with serine residues (Ser64 and Ser315) in the β-lactamase active site. Additionally, recent research has shown that compound 72 inhibits biofilm accountable by Pseudomonas aeruginosa, a resistant Gram-negative bacterium responsible for nosocomial infections. When exposed to SM23 (72), the creation of virulence factors related to biofilm formation, such as pyoverdine and elastase, is significantly inhibited, without the need for antibiotics.[40]



Fiqure 2.11: Compound SM23, an inhibitor of class C β-lactamases.

2.2.6 Antiviral Activity

Boronic acids can effectively bind to carbohydrates, making them valuable in treating viruses like human immunodeficiency virus (HIV), which has a highly glycosylated envelope. This binding ability is linked to their physicochemical properties. HIV-1 causes AIDS, and a crucial RNA sequence known as the Rev response element (RRE) plays a crucial position in the virus's replication. The interaction between the Rev protein and RRE facilitates viral RNA replication, making the Rev-RRE interaction a promising treatment target. Branched peptides (BPs) effectively target the transactivation response element (TAR) associated with HIV RNA and demonstrate low cytotoxicity and good cell permeability. By introducing boronic acid moieties to these BPs, researchers aimed to enhance their affinity for RNA. Synthesis of branched peptide boronic acids (BPBAs) showed increased affinity for RRE, disrupting the Rev-RRE interaction and inhibiting viral replication. Structure-activity relationship (SAR) studies revealed that the presence of boronic acid is crucial for effective binding. BPBA3 emerged as the most promising compound, showing high cellular uptake and strong inhibition of HIV replication in vitro, with an IC50 of about 5 μM. Its binding to RRE suggests a conformational change that may enhance susceptibility to RNase cleavage, aiding in the defense against RNA viruses.[41], [42]

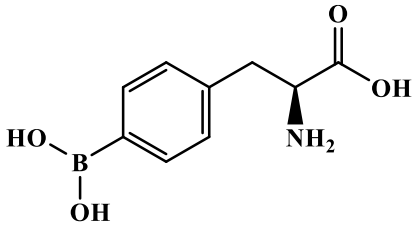


Figure 2.13: BPBA compound, is a disruptor of the Rev-RRE interaction and acts as an inhibitor of HIV-1 replication.

2.2.7 Benzoxaboroles

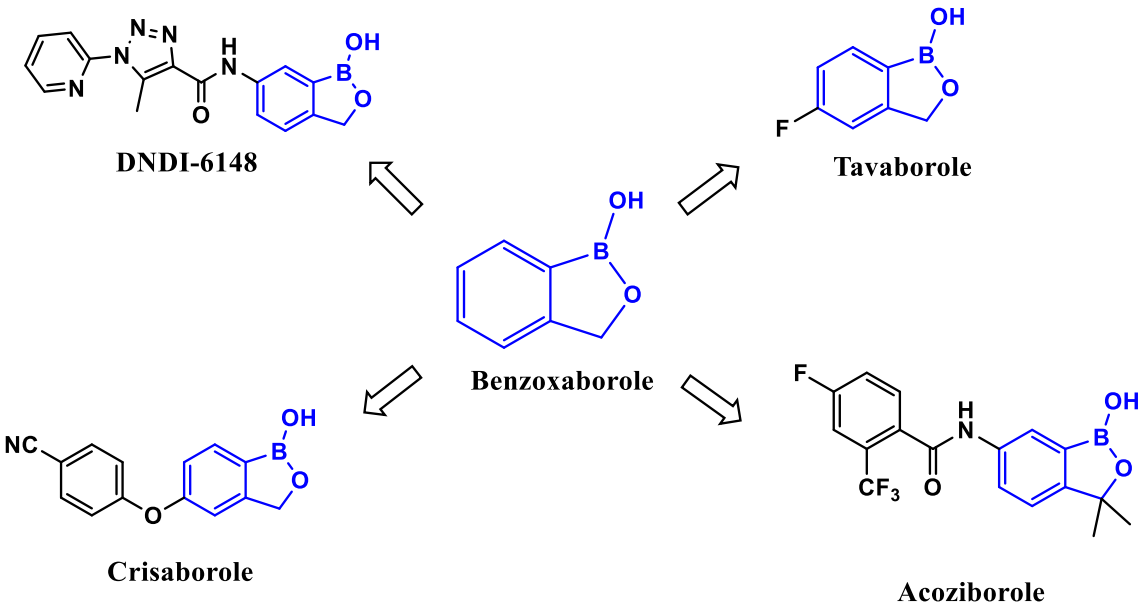
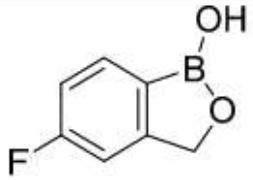
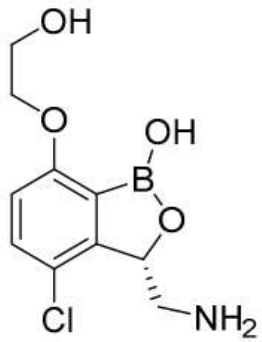
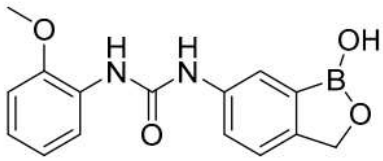
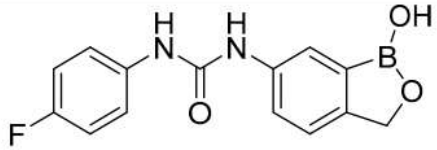
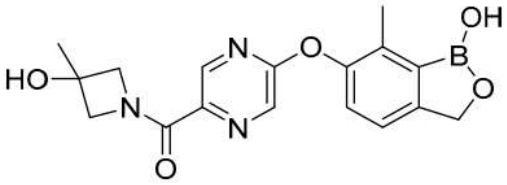
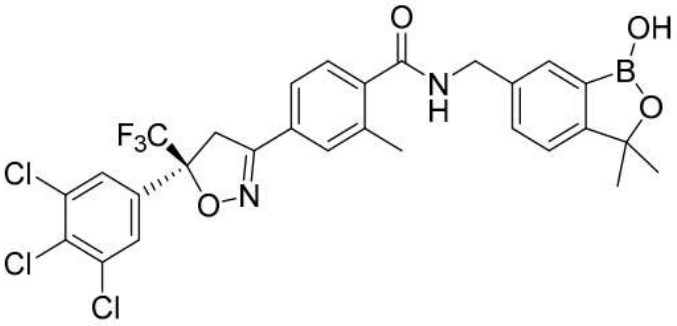
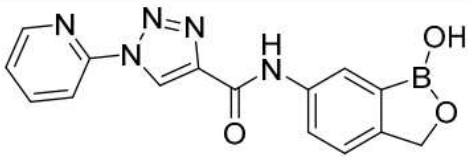


Figure 2.14: Representative Examples of Benzoxaborole

Compounds with a boron atom in a heterocycle joined to an aromatic ring are called benzoxaboroles, and they are recognized for their bioactivity. Since the discovery of the antifungal medication tavaborole, interest in these molecules has increased significantly in the field of medicinal chemistry. Benzoxaboroles are mostly employed for their anti-infective and antiparasitic qualities and are often more soluble than boronic acids. The table below provides a summary of these compounds' recent activity [56].

Compound	Biological Activity
 Tavaborole (**112**)	Drug for treatment of onychomycosis—leucyl-tRNA synthetase inhibitor

	Selective leucyl-tRNA synthetase inhibitor for *Mycobacterium tuberculosis* (*M. tuberculosis*, IC_{50} [1] of 0.2 μM)
 **114**	Selective inhibitor of human carbonic anhydrases (CAs) (*Ki* [2] of 69 -414 nM)
 **115**	Selective inhibitor of β-CA (*Cryptococcus neoformans*, *Ki* of 78 nM; *Candida glabrata*, *Ki* of 75 nM)
	Anti-*Plasmodium* agent (*P. falciparum*, ED_{90} [3] of 0.85 mg/kg) - promising for the treatment of malaria
 **117**	Oral ectoparasiticide agent for *Dermacentor variabilis* (American dog ticks) and *Ctenocephalides felis* (cat fleas) (EC_{50} [4] of 96.6 μM)
 **118**	Topical agent for treatment of cutaneous leishmaniasis (*Leishmania major*, EC_{50} of 4.26 μM; *L.tropica*, EC_{50} of 2.01 μM)

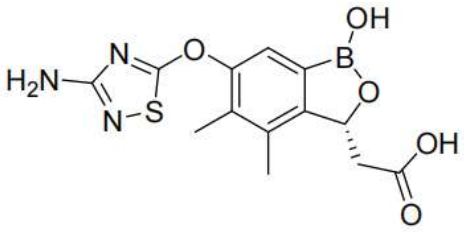
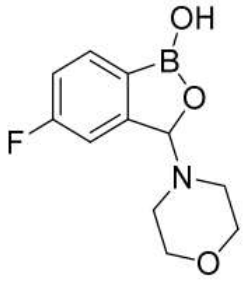
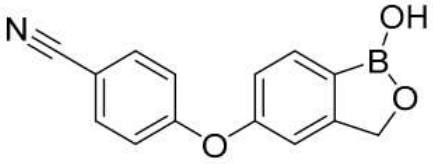
 119	Serine β-lactamase inhibitor (Class A, IC_{50} < 0.005–0.026 μM; Class C, IC_{50} of 0.012–0.067 μM; Class D, IC_{50} of 0.088–0.12 μM) of pathogens such as *E. coli* (MIC [5] of 0.25–1 μg/ml)
 120	Antiproliferative and proapoptotic agent for ovarian cancer line cell A2780 (IC_{50} of 14.8 μM)
 Crisaborole (**121**)	Topical anti-inflammatory drug for atopic dermatitis—phosphodiesterase type 4 (PDE4) inhibitor promising for psoriasis

Table 2.1 Biological activity of derivatives of benzoxaboroles

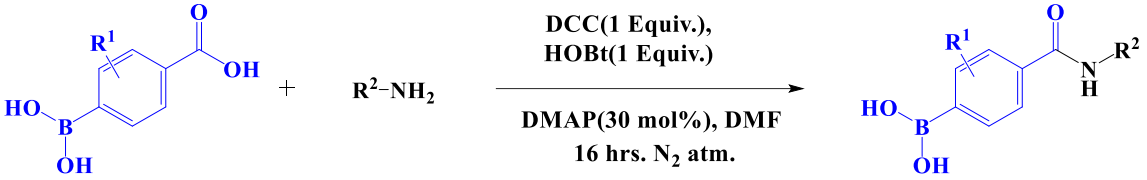
Research objectives

- The objective is to design, synthesis and study of various acyclic boronic acid pharmaceutical drug candidates through the modification of functional groups, thereby enhancing their functionalization potential. Through this process, we seek to create a diverse range of acyclic boronic acid derivatives with unique chemical properties and functionalities.
- we strategically introduced specific functional groups into the molecular structure of our desired product. These functional groups are chosen based on their compatibility with known late-stage functionalization reactions.

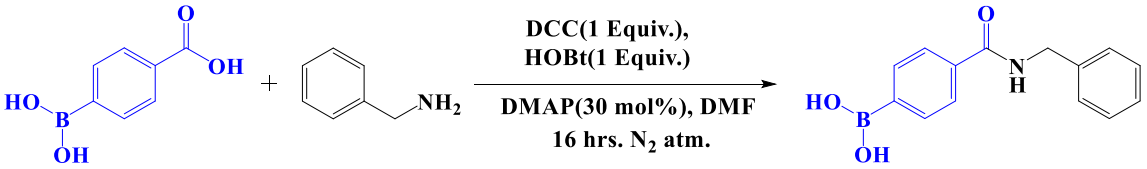
CHAPTER 3: RESULTS AND DISCUSSION, REACTION MECHANISMS, CONCLUSION AND EXPERIMENTAL PROTOCOLS

Initially we have synthesized Compound A from commercially available **4-carboxy phenyl boronic acid** and benzylamine in the presence dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) as coupling reagents. DCC activates the carboxylic acid group, allowing for a more reactive intermediate, while HOBt helps prevent side reactions and increases the yield of the desired product. Additionally, we included 4-(dimethylamino)pyridine (DMAP) in the reaction mixture. DMAP acts as a catalyst that enhances the acylation process by accepting protons, thereby increasing the nucleophilicity of the amine. The 4-carboxy phenyl boronic acid is soluble in DMF, not in DCM. DCC and HOBt are often used together as coupling reagents, while DMAP is a catalyst for acylation reactions.

Scheme 3.1: General reaction mechanism



Scheme 3.2: Synthesis of (4-(benzylcarbamoyl)phenyl)boronic acid from 4-Carboxy phenylboronic acid



For the selection of best conditions for this reaction, we did the optimization for solvent ,base with additives.

OPTIMIZATON TABLE

Sl. No.	Reagent	Additive	Solvent	Base	Yield%
1	DCC	HOBt	Ethyl acetate	DIPEA	Less
2	DCC	HOBt	Ethyl acetate	Et3N	Less
2	DCC	HOBt	Ethyl acetate	Piperidne	Less
3	DCC	HOBt	Ethyl acetate	DMAP	10%
4	DCC	HOBt	Ethyl acetate	Morpholine	Less
5	DCC	HOBt	Chloroform	DMAP	Less
6	DCC	HOBt	Water	DMAP	10
7	DCC	HOBt	Dichloromethane	DMAP	
8	DCC	HOBt	N,N-Dimethylformamide	DMAP	Up to **70%**
9	DCC	HOBt	Tetrahydrofuran	DMAP	20
10	DCC	HOSu	N,N-Dimethylformamide	DMAP	10
11	CDI	HOBt	N,N-Dimethylformamide	DMAP	10

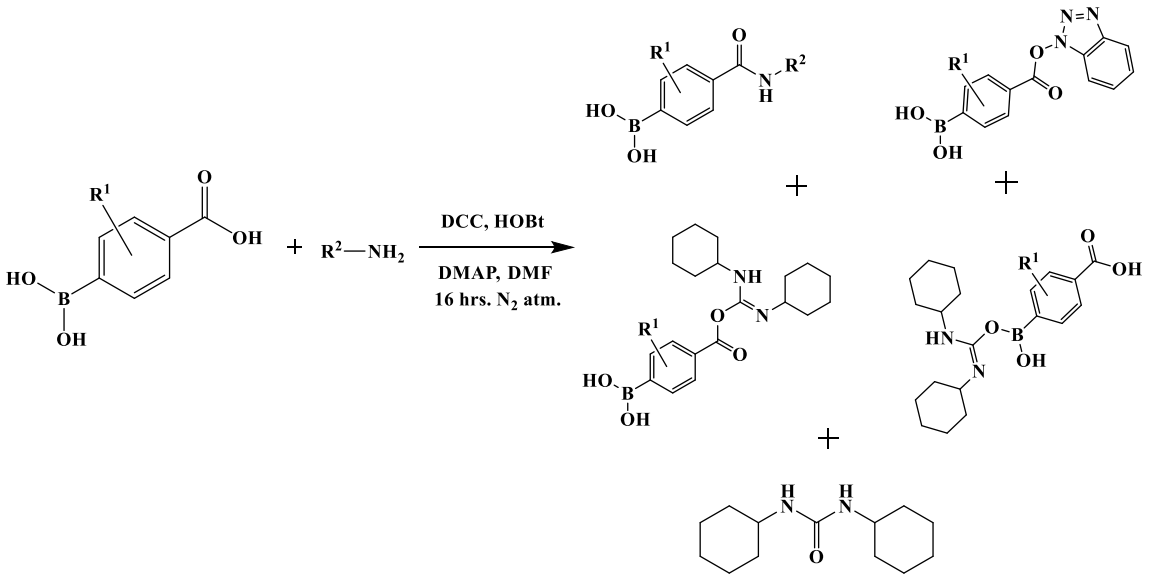
Table 3.1: Optimization table

When we were doing the optimization of the solvent, we put the reaction in different solvents and then we understood that the DMF is giving the maximum yield. The water,CHC3,DCM are insoluble in our substrate. The substrate is soluble in ethyl acetate,

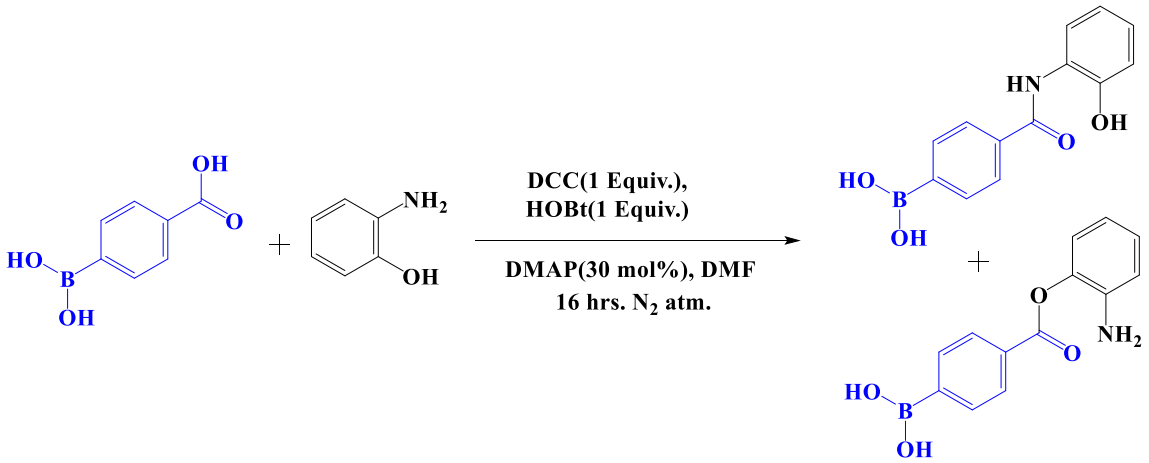
but the yield is less, and soluble in MeOH also, but MeOH is a reactive solvent, so we didn't consider MeOH.

There are a lot of undesirable other products are also forming, while checking the TLC, more spots are showing, this may be because of the side reactions and DCC coupling with OH present on the boron atom.

Undesirable Products and side Product Forms in DCC coupling reaction



Scheme 3.3: Undesirable Products and side Product Forms in DCC coupling reaction



Scheme 3.4: Synthesis of (4-((2-hydroxyphenyl)carbamoyl)phenyl)boronic acid from 3-Carboxy-5-nitrophenylboronic acid

Then we have further expanded this scheme for the synthesis of derivatives by changing the amine. We have selected the amines on the basis of it should be different sets of amine. So we choose primary aromatic amines, aliphatic amines, amino acids, chiral amine etc.

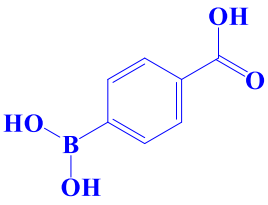
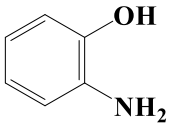
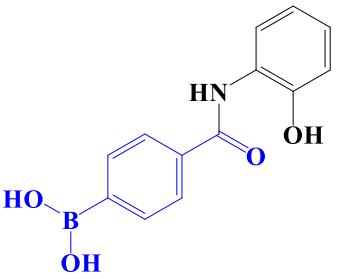
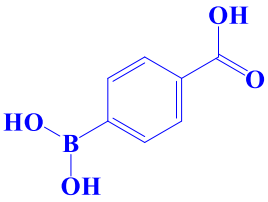
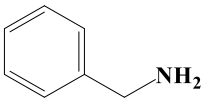
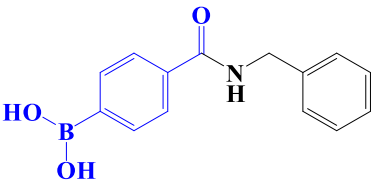
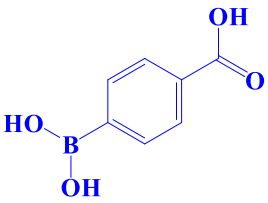
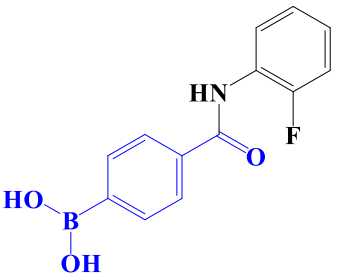
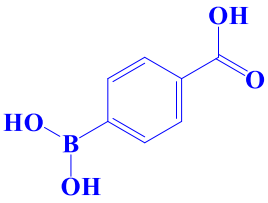
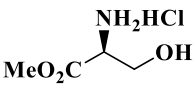
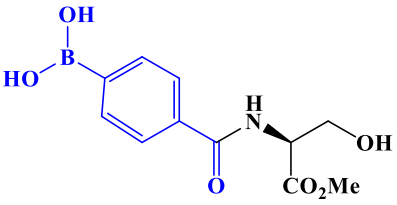
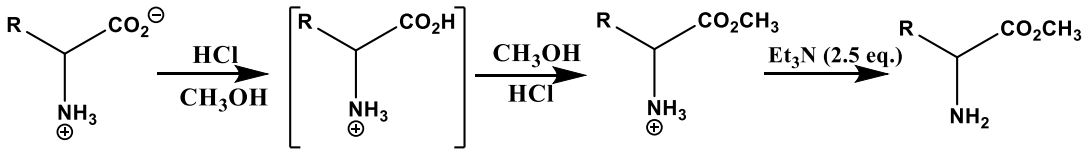
Sl. No.	Boronic acid	Amine	Synthesized Boronate Derivatives	Yields
1	 1	 2a	 **3a**	**52%**
2		 2b	 **3b**	**68%**
3		2c	 **3c**	**64%**
4		 2d	 **3d**	**59%**

Table 3.2 Synthesis of corresponding amides

When preparing for the DCC coupling reaction involving amino acids such as serine and tyrosine, it is important to protect the carboxylic acid group. To achieve this, amino acids

can be converted into esters through a process called esterification. This reaction typically involves the carboxylic acid group of the amino acid reacting with an alcohol in the presence of an acid catalyst. The result of this reaction is an ester and water as byproducts. Once the amino acid ester is produced, it is then reacted with 4-carboxyphenylboronic acid in DCM solvent, along with DCC, HOBt, and DMAP, under a nitrogen atmosphere for a duration of 16 to 24 hours.



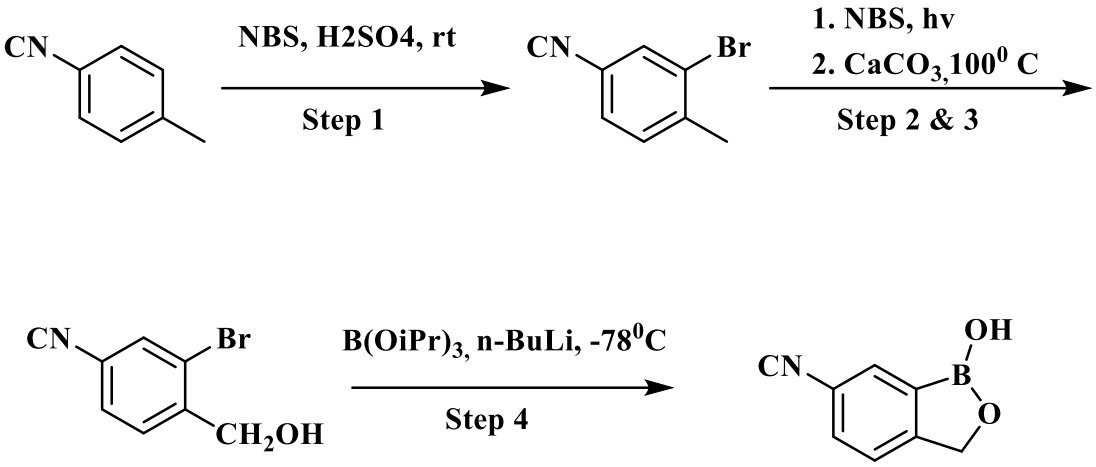
Scheme 3.5: Esterification of Aminoacids

Initially, we focused on synthesizing various amides using 4-carboxyphenylboronic acid in conjunction with different amines. Following this stage, we turned our attention to **3-carboxy-5-nitrophenylboronic acid**. This compound was then reacted with an array of different amines under the same reaction conditions. The entire reaction was carried out in a solution of N,N-dimethylformamide (DMF), which provided a suitable solvent environment to facilitate the coupling reactions. Through these systematic approaches, we aimed to obtain a series of new amide compounds for further study.

We carefully considered the structural and functional compatibility of the amines with the nitrated boronic acid to achieve our desired final products. Among the selected amines, we also incorporated a chiral amine to explore the potential for enantioselective outcomes in the reaction. This systematic approach aims to broaden the scope of our research and enhance the diversity of amide derivatives obtained from our reactions.

Further we synthesized 3-((2-hydroxybenzyl)amino)-5-((1-phenylethyl)carbamoyl) phenylboronic acid by the Reductive amination, **Reductive amination** begins with an amine attacking a carbonyl compound to form a carbinolamine intermediate. This intermediate then dehydrates to yield an imine (with a primary amine) or an iminium ion (with a secondary amine). A reducing agent like Sodium borohydride ($NaBH_4$) or sodium cyanoborohydride ($NaBH_3CN$) then reduces the imine or iminium ion to form the corresponding amine. The reaction is performed under mildly acidic or neutral conditions to promote imine formation and prevent over-reduction, allowing for efficient C–N bond formation.

3.2 Synthesis of 6-Amino-1-hydroxy-2,1-benzoxaborolane



Scheme: Synthesis of 6-Amino-1-hydroxy-2,1-benzoxaborolane

We performed the reaction from step 3 (2-bromo-4-isocyanophenyl)methanol to step 4 6-isocyanobenzo[c][1,2]oxaborol-1(3H)-ol in presence of n-BuLi and we tried with different temperature. Ie, 0 ^{0}C,-30 ^{0}C, -78 ^{0}C,etc. we got the best yield with -78 ^{0}C.

Sl. No.	Solvent	temperatrure	Yield%
1	THF	0 ^{0}C	10
2	THF	-30 ^{0}C	20
3	THF	-78 ^{0}C	70
4	DCM	-78 ^{0}C	30
5	DMF	-78 ^{0}C	10
6	DMSO	-78 ^{0}C	5

Table 3.3: Optimization table

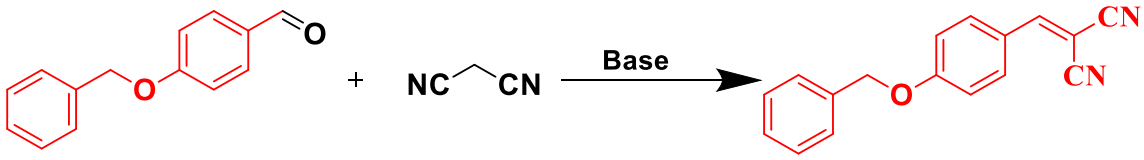
We have synthesized the key intermediate, 6-cyano-1-hydroxy-2,1-benzoxaborolane from commercially available 4-tolunitrile using an established protocol. This four-step sequence displayed reliable outcomes on decagram scales, yielding 6-amino-1-hydroxy-2,1-benzoxaborolane with a 40% overall yield from 4-tolunitrile. This

approach avoids the costly starting material and hazardous nitration, but further optimization is needed to eliminate the need for column chromatography.

3.3 Synthesis Of Oxasilacycles by Silicon incorporation in THF moieties;

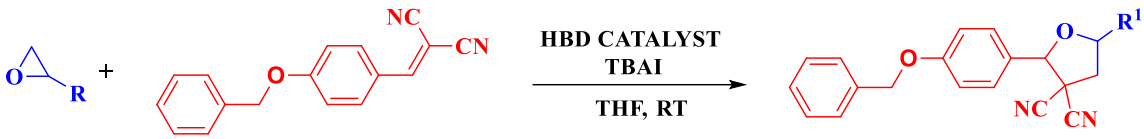
3.3.1 Synthesis of Electrophile

First we synthesized the dicyano electrophile, ie, 2-(4-(benzyloxy)benzylidene) malononitrile from commercially available 4-(benzyloxy)benzaldehyde ,by reacting with malanonitrile in presence of base. We use 1-Methylimidazole as base.



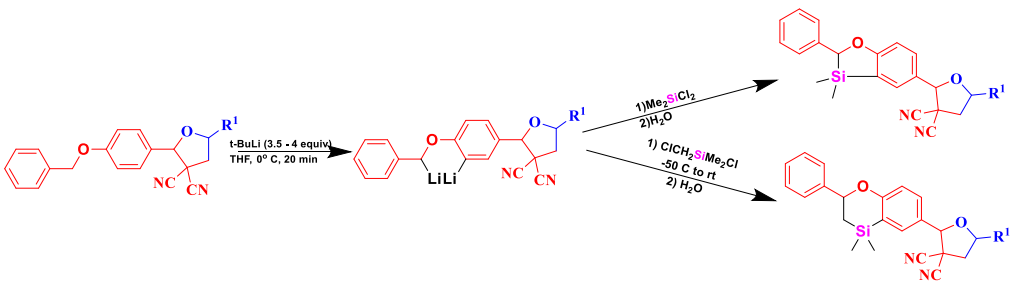
<u>Reaction of Epoxide ring and Dicyano electrophile</u>.

Then we reacted it with our synthesized epoxide 2-phenyloxirane, in presence of HBD catalyst and TBAI in room temperature to form corresponding dicyano electrophile, ie, 2-(4-(benzyloxy)benzylidene).



<u>Synthesis Of Oxasilacycles</u>

At low temperatures, aryl benzyl ethers undergo α-lithiation with t-BuLi to produce the α-lithiobenzyloxy group. Also it facilitates access to o-lithiophenyl α-lithiobenzyl ethers by acting as a directed metalation group (DMG). Methoxy groups at the meta location increase this ortho-directing effect.

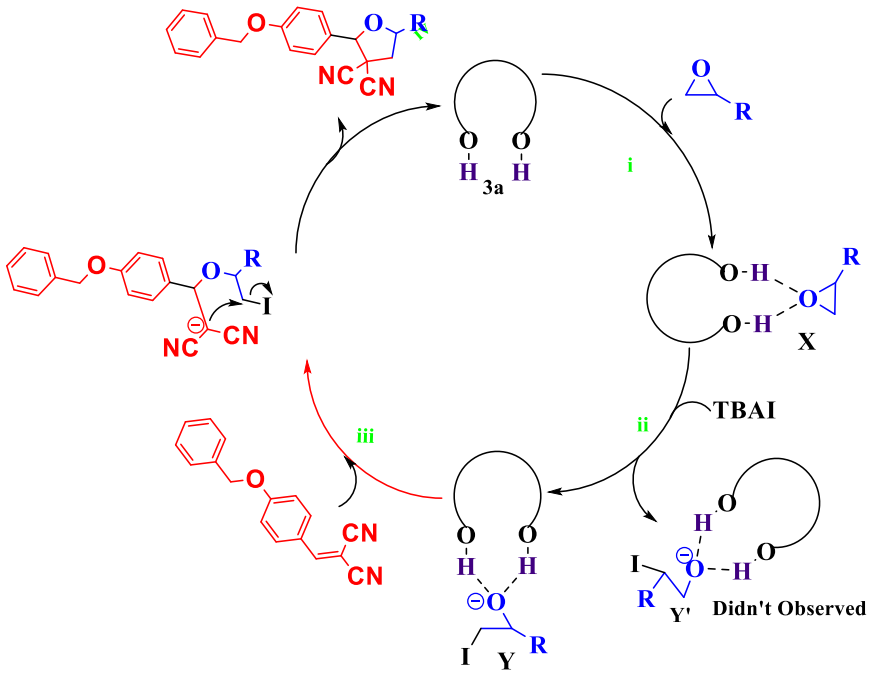


Sl. No.	Solvent	temperatrure	Yield%
1	THF	0 ^{0}C	Reaction is not going
2	THF	-30 ^{0}C	Reaction is not going
3	THF	-78 ^{0}C	Multiple spots are forming

Table 3.4: Optimization table for the oxasilacycle synthesis

We have performed this reaction in different conditions with n-BuLi, but we could not get our desired products, as multiple spots were formed. We are not able to use t-BuLi due to its high reactive nature, handling in lab is difficult.

Reaction mechanism:



3.2.1 Experimental Procedures

3.2.1.1 General procedure 1: Synthesis of (4-(benzylcarbamoyl)phenyl)boronic acid from 4-carboxyphenylboronic acid (Scheme 3.1 and 3.2)

In a 25 mL two-neck round-bottom flask with a magnetic stir bar, dissolve 4-carboxyphenylboronic acid (1.0 equiv.) in N,N-dimethylformamide (DMF) and cool to 0–5 °C under nitrogen with continuous stirring. Add dicyclohexylcarbodiimide (DCC) (1.0 equiv.) and 1-hydroxybenzotriazole (HOBt) (1.0 equiv.) sequentially, stirring for 15 minutes. Then, add the corresponding amine (1.0 equiv.) and 4-(dimethylamino)pyridine (DMAP) (30 mol%). Remove the ice bath and allow the reaction to proceed at room temperature for 16 hours, or until TLC shows complete consumption of the starting material. Evaporate the solvent (mostly DCM) under reduced pressure, then perform liquid-liquid extraction with ethyl acetate and water. Separate the organic layer, dry it with Na_2SO_4, filter, and concentrate. Purify the crude product by column chromatography using chloroform and methanol (9.5:0.5) as the eluent to obtain the desired compound in pure form.

3.2.1.2 Synthesis of corresponding carbamoylphenyl boronic acid from 2-Aminophenol (scheme 3.4)

In a 25 mL two-neck round-bottom flask with a magnetic stir bar, 3-carboxy-5-nitrophenylboronic acid (1.0 equiv.) was dissolved in N,N-dimethylformamide (DMF) and cooled to 0–5 °C under nitrogen while stirring. Dicyclohexylcarbodiimide (DCC) (1.0 equiv.) and 1-hydroxybenzotriazole (HOBt) (1.0 equiv.) were added sequentially and stirred for 15 minutes. Then, 2-aminophenol (1.0 equiv.) and 4-(dimethylamino)pyridine (DMAP) (30 mol%) were added, and the reaction was allowed to proceed at room temperature for 16 hours, monitored by thin-layer chromatography (TLC). After the reaction, the solvent (primarily DCM) was evaporated under reduced pressure. The crude product underwent liquid-liquid extraction with ethyl acetate and water, and the organic layer was dried with anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated. Finally, purification by column chromatography using chloroform and methanol (0.9:0.1) yielded the desired compound 2 in pure form.

3.2.1.3 Esterification of Amino acids (Scheme 3.5)

In a 25 mL two-neck round-bottom flask (RB) equipped with a magnetic stir bar, we added 3-carboxy-5-nitrophenylboronic acid (1.0 equivalent) and dissolved it in N,N-dimethylformamide (DMF). The reaction mixture was then cooled to 0–5 °C under a nitrogen atmosphere while continuously stirring.

Next, we sequentially added dicyclohexylcarbodiimide (DCC) (1.0 equivalent) and 1-hydroxybenzotriazole (HOBt) (1.0 equivalent) to the cooled solution. After stirring for 15 minutes, we added the corresponding 2-aminophenol (1.0 equivalent) along with 4-(dimethylamino)pyridine (DMAP) (30 mol%). The ice bath was then removed, and the reaction was allowed to proceed at room temperature for 16 hours, or until TLC analysis indicated complete consumption of the starting material.

Upon completion, we evaporated the solvent, primarily DCM, under reduced pressure. The crude product was then subjected to liquid-liquid extraction using ethyl acetate and water. We separated the organic layer, dried it over anhydrous Na_2SO_4, filtered it, and concentrated it under reduced pressure. Finally, the resulting crude product was purified by column chromatography using a mixture of chloroform and methanol (0.9:0.1) as the eluent, yielding the desired compound in a pure state.

3.2.1.4 Reduction of 3-nitro-5-((1-phenylethyl) carbamoyl)phenyl boronic acid to 3-amino-5-((1-phenylethyl)carbamoyl) phenylboronic acid (Scheme 3.9)

3-Nitro-5-((1-phenylethyl)carbamoyl)phenylboronic acid (1.0 equiv.) was selectively reduced to yield the corresponding amine derivative. The reaction involved stirring the nitro compound with hydrazine hydrate (2.0 equiv.) and formic acid (2.0 equiv.) in the presence of a catalytic amount of zinc powder (approximately a pinch) at 100 °C for 8 hours. The progress of the reaction was monitored using thin-layer chromatography (TLC). Once the reaction was complete, the mixture was allowed to cool to room temperature. Subsequently, 20 mL of ethyl acetate was added, and the mixture was washed with distilled water. The organic layer (ethyl acetate) was then separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product.

3.2.1.5 General procedure 5: Synthesis of (3-(2-hydroxybenzamido)-5-((1-phenylethyl) carbamoyl) phenyl)boronic acid (Scheme 3.10)

A 25 mL two-neck round-bottom flask was prepared by dissolving salicylic acid (1.0 equivalent) in N,N-dimethylformamide (DMF). The mixture was cooled to 0–5 °C under a nitrogen atmosphere with stirring. Dicyclohexylcarbodiimide (DCC) (1.0 equivalent) and 1-hydroxybenzotriazole (HOBt) (1.0 equivalent) were added sequentially and stirred for 15 minutes. Then, 3-amino-5-((1-phenylethyl)carbamoyl)phenylboronic acid (1.0 equivalent) and 4-(dimethylamino)pyridine (DMAP) (30 mol%) were added. The reaction proceeded at room temperature for 24 hours, or until TLC indicated complete consumption of the starting material. Afterward, the solvent DCM was evaporated under reduced pressure. The crude product underwent liquid-liquid extraction with ethyl acetate and water, followed by drying over anhydrous Na_2SO_4. It was then filtered and concentrated. Finally, the crude product was purified by column chromatography using chloroform and methanol (0.9:0.1) as the eluent, yielding the desired compound 2 in pure form.

3.2.1.6 Synthesis of 3-((2-hydroxybenzyl)amino)-5-((1-phenylethyl)carbamoyl) phenylboronic acid via Reductive Amination (Scheme 3.11)

The target compound, 3-((2-hydroxybenzyl)amino)-5-((1-phenylethyl)carbamoyl) phenylboronic acid, was synthesized using reductive amination. First, 3-amino-5-((1-phenylethyl)carbamoyl)phenylboronic acid was reacted with salicylaldehyde (1.0 equivalent) in methanol, with triethylamine (1.5 equivalents) to facilitate imine formation. The mixture was stirred at room temperature until TLC analysis confirmed imine formation and complete consumption of the starting material. Next, sodium borohydride ($NaBH_4$, 2.5 equivalents) was added to reduce the imine to the secondary amine. The reaction mixture underwent standard aqueous work-up, and the crude product was purified to obtain the desired compound.

CONCLUSIONS

We have successfully synthesized carbamoyl phenylboronic acid derrivatives employing sophisticated synthetic methodologies including late-stage functionalized and divergent-oriented synthesis. Our synthesis strategies allowed for the efficient and strategic introduction of functional groups without disturbing the functional groups. By harnessing the principles of late-stage functionalization, we were able to modify pre-existing complex molecules, enabling rapid diversification and access to structurally intricate compounds. Additionally, we have done **in-vitro** study with respect to **BlaC (enzyme)** with our synthesize molecules and we get potential inhibiting activity of our compounds. The successful synthesis of these compounds was confirmed through rigorous characterization using advanced analytical techniques such as IR spectroscopy, and NMR spectroscopy.

CHAPTER 4: EXPERIMENTAL DATA AND REFERENCES

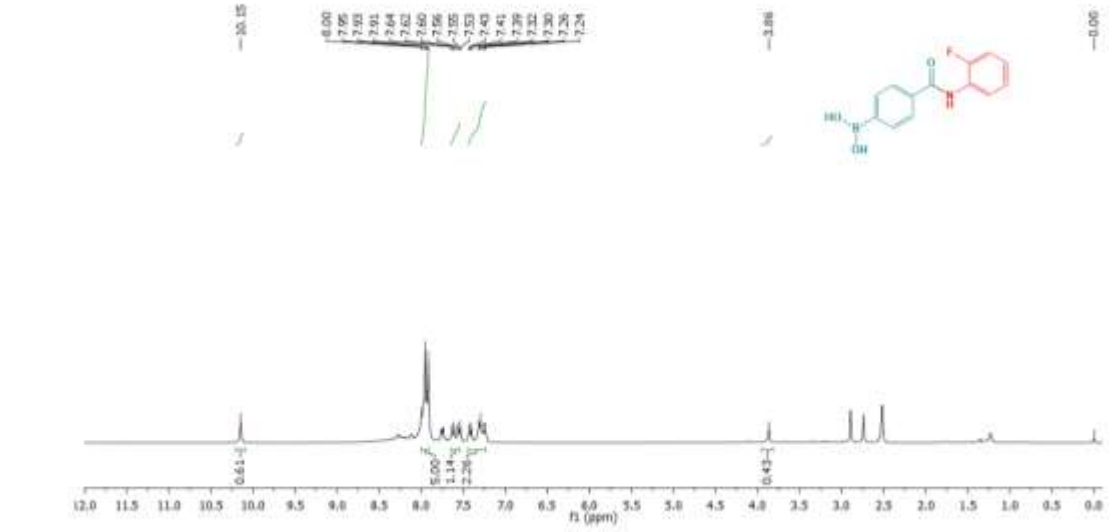
4.1 Experimental Data

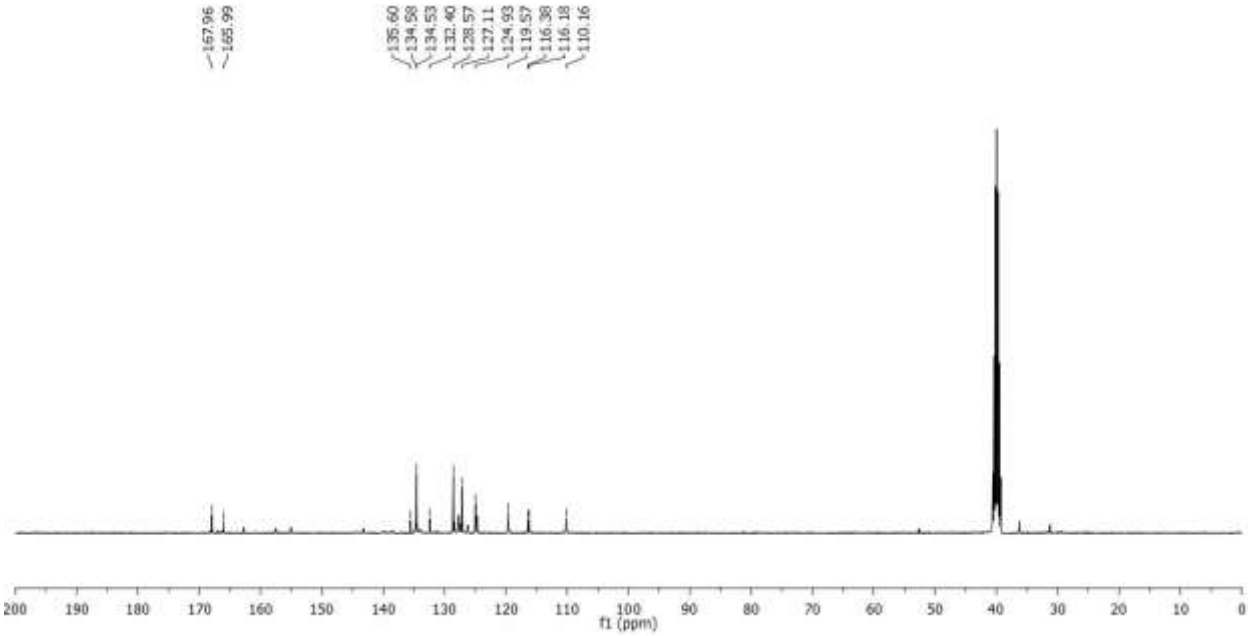
4.1.1 Synthesis of (4-((2-fluorophenyl)carbamoyl)phenyl)boronic acid.

A mixture of 4-carboxyphenylboronic acid (1.0 equiv.) in N,N-dimethylformamide (DMF) was cooled to 0–5 °C under nitrogen with continuous stirring. Dicyclohexylcarbodiimide (DCC) (1.0 equiv.) and 1-hydroxybenzotriazole (HOBt) (1.5 equiv.) were added sequentially and stirred for 15 minutes. Then, 2-fluoroaniline (1.0 equiv.) and 4-(dimethylamino)pyridine (DMAP) (30 mol%) were added. The ice bath was removed, allowing the reaction to proceed at room temperature for 16 hours, or until TLC indicated complete consumption of the starting material. Afterward, the primary solvent, DCM, was evaporated under reduced pressure. The crude product was extracted with ethyl acetate and water, the organic layer was dried with anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated. Finally, the crude product was purified by column chromatography using a chloroform-methanol mixture (9.5:0.5) as the eluent..

Experimental Data of (4-((2-fluorophenyl)carbamoyl)phenyl)boronic acid.

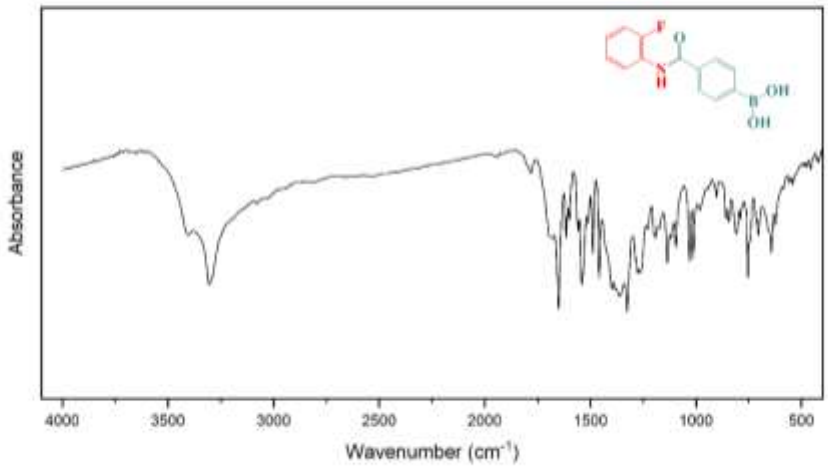
The general procedure outlined above was followed when 4-Carboxyphenylboronic acid (90 mg, 0.5424 mmol) reacted with 2-fluoroaniline (60.27 mg, 0.5424 mmol) at a temperature of 0-5 °C. This reaction occurred in the presence of DCC (111.91 mg, 0.5424 mmol) and HOBt (73.28 mg, 0.5424 mmol) in DMF solvent (2.5 mL) to yield the corresponding product, 4-((2-fluorophenyl)carbamoyl)phenyl)boronic acid (191.66 mg), resulting in a 74% yield.; IR $\tilde{\nu}_{max}$ (KBr, cm−1):1134, 1188, 1280, 1324, 1367, 1401, 1457, 1490, 1543, 1562, 1601, 1616, 1653, 1672, 1780, 3311, 3422; ; ^{1}H NMR (400 MHz, DMSO) δ 10.15 (s, 1H), 8.00 – 7.91 (m, 5H), 7.65 – 7.54 (m, 1H), 7.43-7.24 (m, 2H), 3.86 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.96, 165.99, 135.60, 134.58, 134.53, 132.40, 128.57, 127.11, 124.93, 119.57, 116.28, 110.16.





^{13}C NMR (101 MHz, DMSO) δ 167.96 (s), 165.99 (s), 135.60 (s), 134.55 (d, *J* = 5.0 Hz), 132.40 (s), 128.57 (s), 127.11 (s), 124.93 (s), 119.57 (s), 116.28 (d, *J* = 19.9 Hz), 110.16 (s).

IR Data graph of **(4-((2-fluorophenyl)carbamoyl)phenyl)boronic acid**

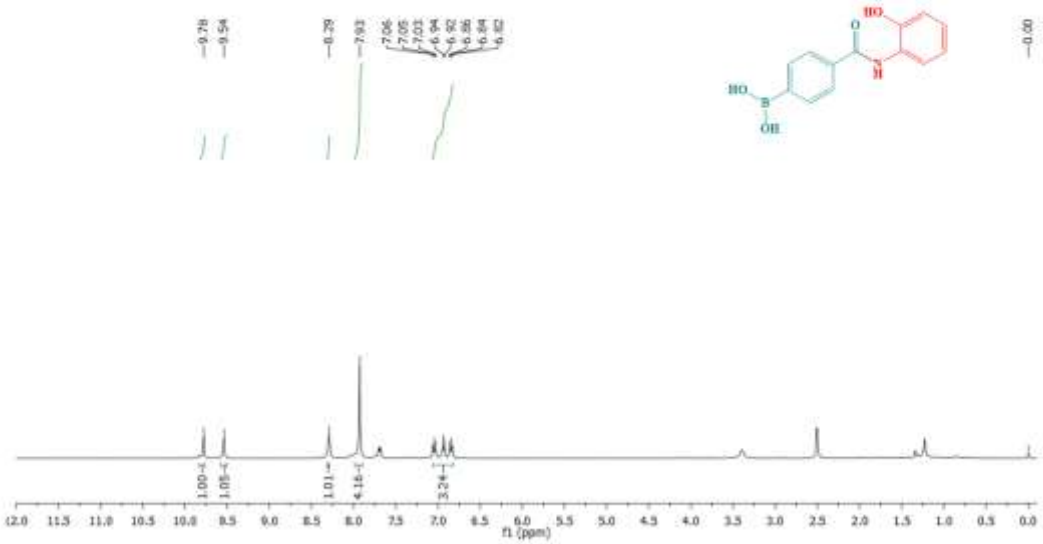


4.1.2 Synthesis of (4-((6-hydroxycyclohexa-1,5-dien-1-yl)carbamoyl)phenyl)boronic acid

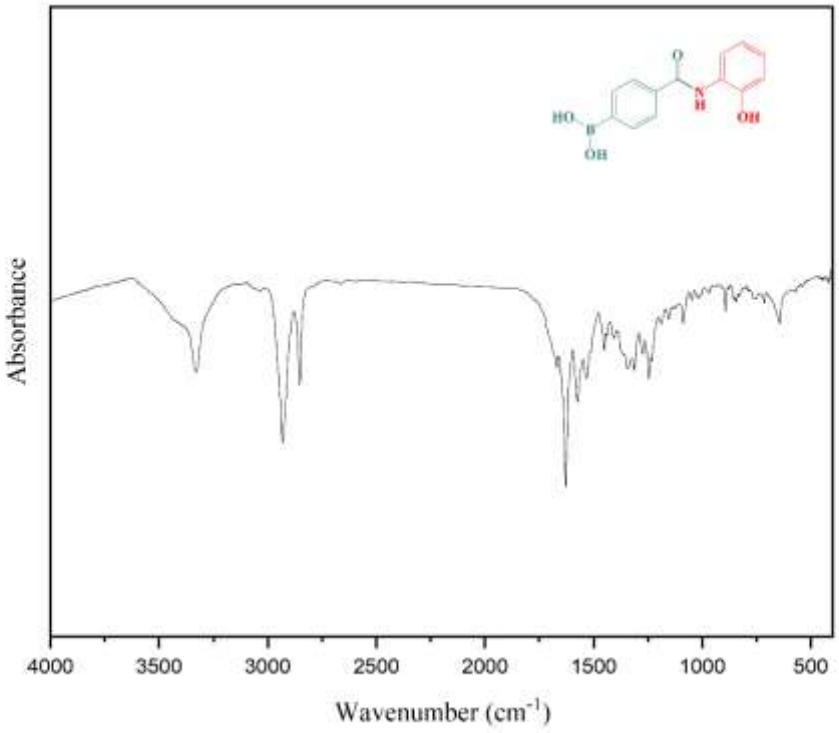
A reaction mixture of 4-carboxyphenylboronic acid (1.0 equiv.) dissolved in N,N-Dimethylformamide (DMF) was cooled to 0–5 °C under nitrogen while stirring. Dicyclohexylcarbodiimide (DCC) (1 equivalent) and 1-hydroxybenzotriazole (HOBt) (1 equivalent) were added, followed by stirring for 15 minutes. Next, 2-fluoroaniline (1.0 equivalent) and 4-(dimethylamino)pyridine (DMAP) (30 mol%) were added. After removing the ice bath, the reaction proceeded at room temperature for 16 hours or until TLC indicated completion. Following the reaction, the solvent (primarily dichloromethane) was evaporated under reduced pressure. The crude product underwent liquid-liquid extraction with ethyl acetate and water, was dried with anhydrous sodium sulfate, filtered, and concentrated. Purification was achieved via column chromatography using chloroform and methanol (9.5:0.5) as the eluent.Experimental Data of (4-((6-hydroxycyclohexa-1,5-dien-1-yl)carbamoyl)phenyl)boronic acid. The general procedure described above was followed when 4-Carboxyphenylboronic acid (80 mg, 0.3088 mmol) reacted with 2-aminophenol (33.70 mg, 0.3088 mmol) at 0-5 0C in the presence of DCC (63.72 mg, 0.3088 mmol) and the HOBt (41.72 mg, 0.3088 mmol) in the DMF (2.5 mL) solvent to afford the corresponding product **(4-((6-hydroxycyclohexa-1,5-dien-1-yl)carbamoyl)phenyl)boronic acid** (133.66 mg, 52% yield; IR νmax̃ (KBr, cm−1

):640,849,894,1091, 1149, 1191, 1229, 1248, 1269, 1314, 1348, 1362, 1405, 1434, 1446, 1538, 1570, 1627, 1671, 2850, 2931, 3326, 3430;

739, 783, 814, 899, 1014, 1029, 1100, 1151, 1178, 1220, 1267, 1334, 1492, 1495, 1538, 1558, 1599, 1633, 1766, 2607, 2726, 2851, 2921, 3072, 3086, 3302, 3383;



^{1}H NMR (400 MHz, DMSO) δ 9.78 (s, 1H), 9.54 (s, 1H), 8.29 (s, 1H), 7.93 (s, 4H), 7.06 – 6.82 (m, 3H).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2000
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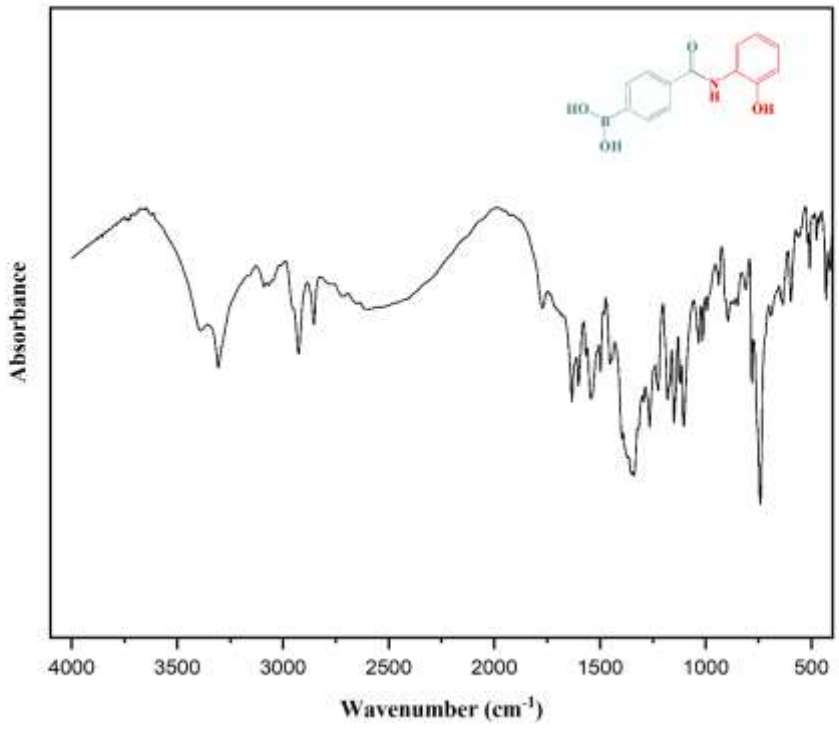
Wavenumber (cm-1)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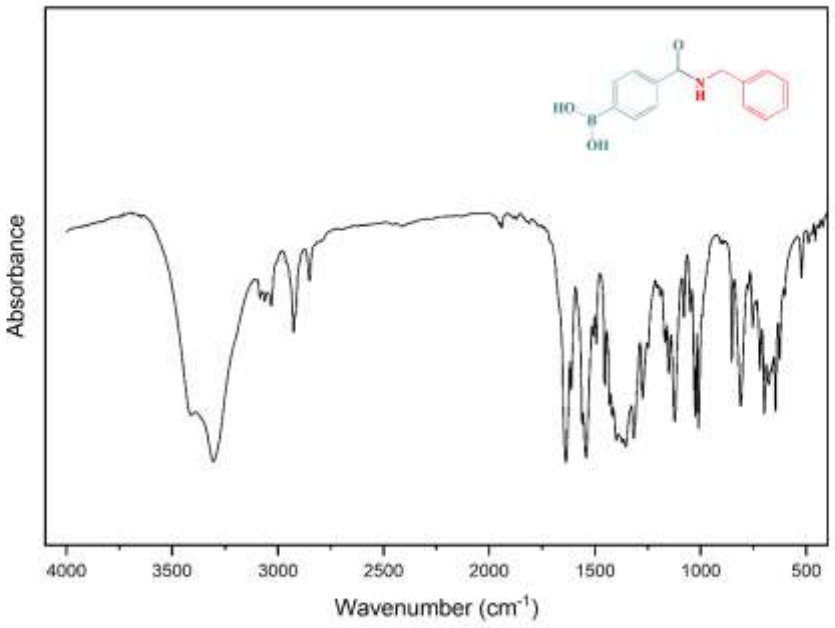
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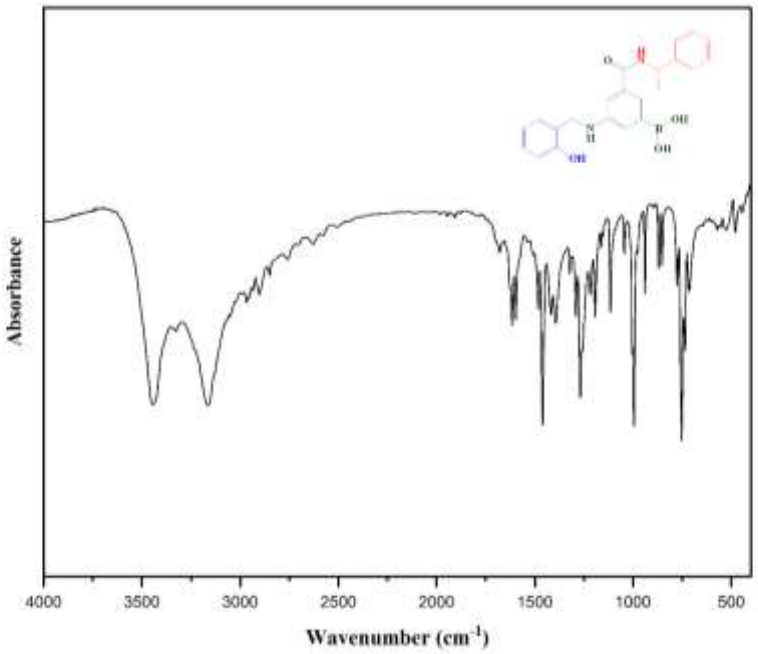
Wavenumber (cm-1)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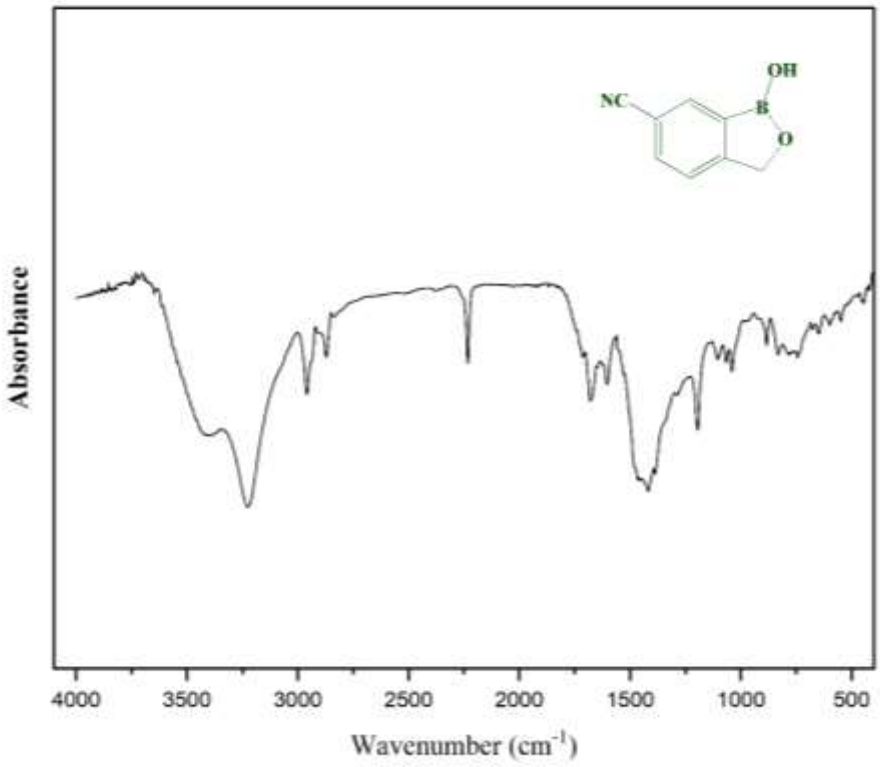
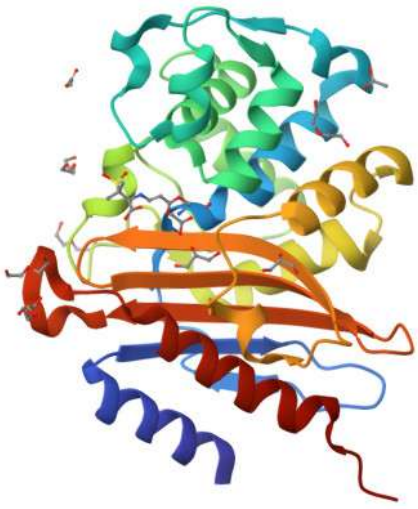
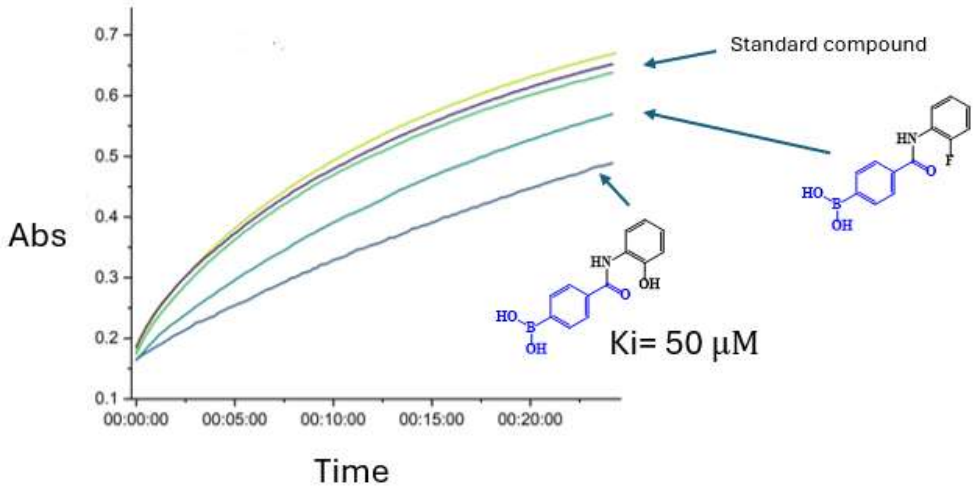
Wavenumber (cm-1)



Time-dependent inactivation of BlaC (enzyme)



3D Structure of BlaC from Mycobacterium tuberculosis



Kinetic studies of the interactions of BlaC (enzyme) with 3a and 3c

Hydrolysis rates in the presence and absence of 3a (dark blue) and 3c (green)

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